Tubo-ovarian Serous Tumours

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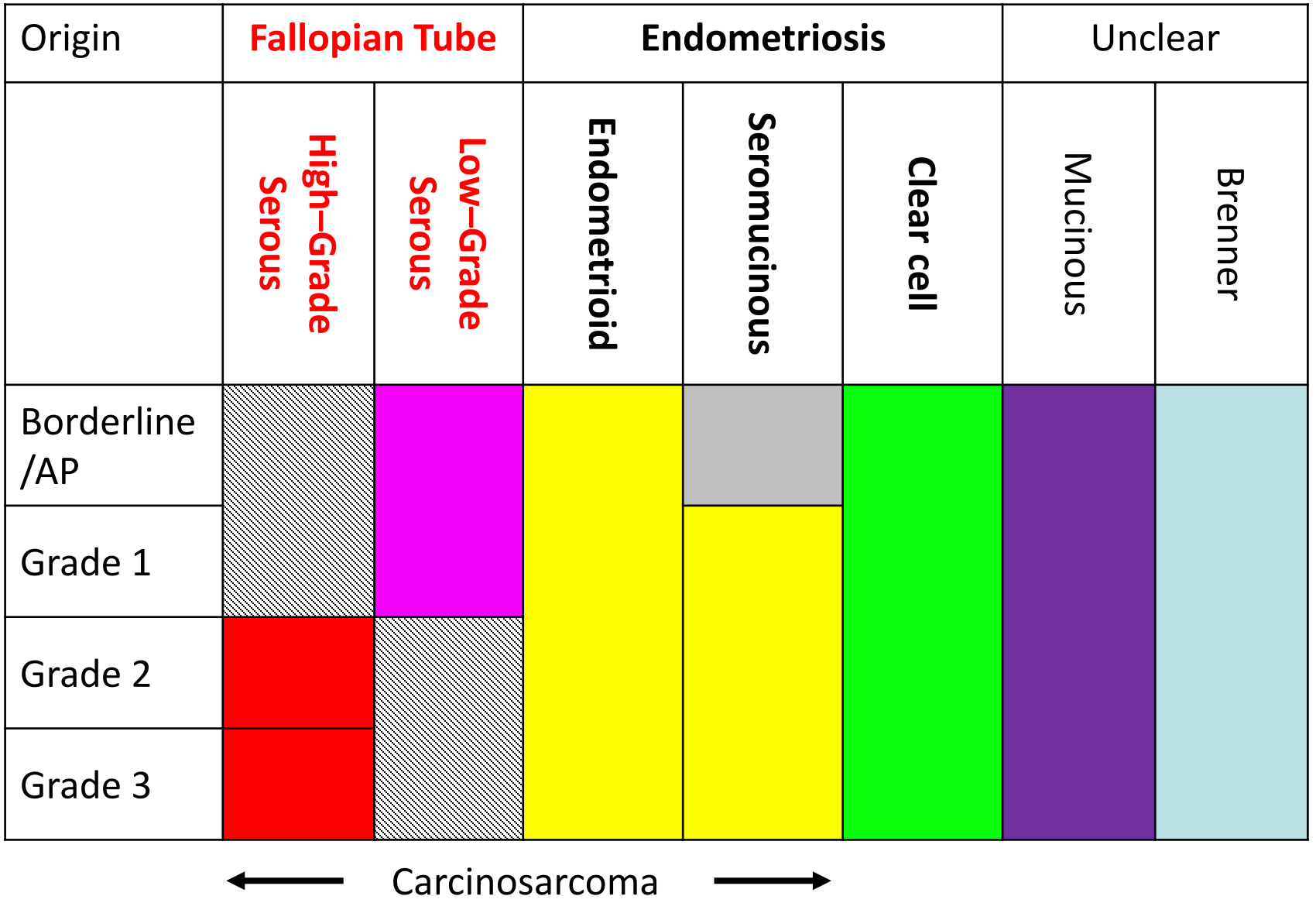
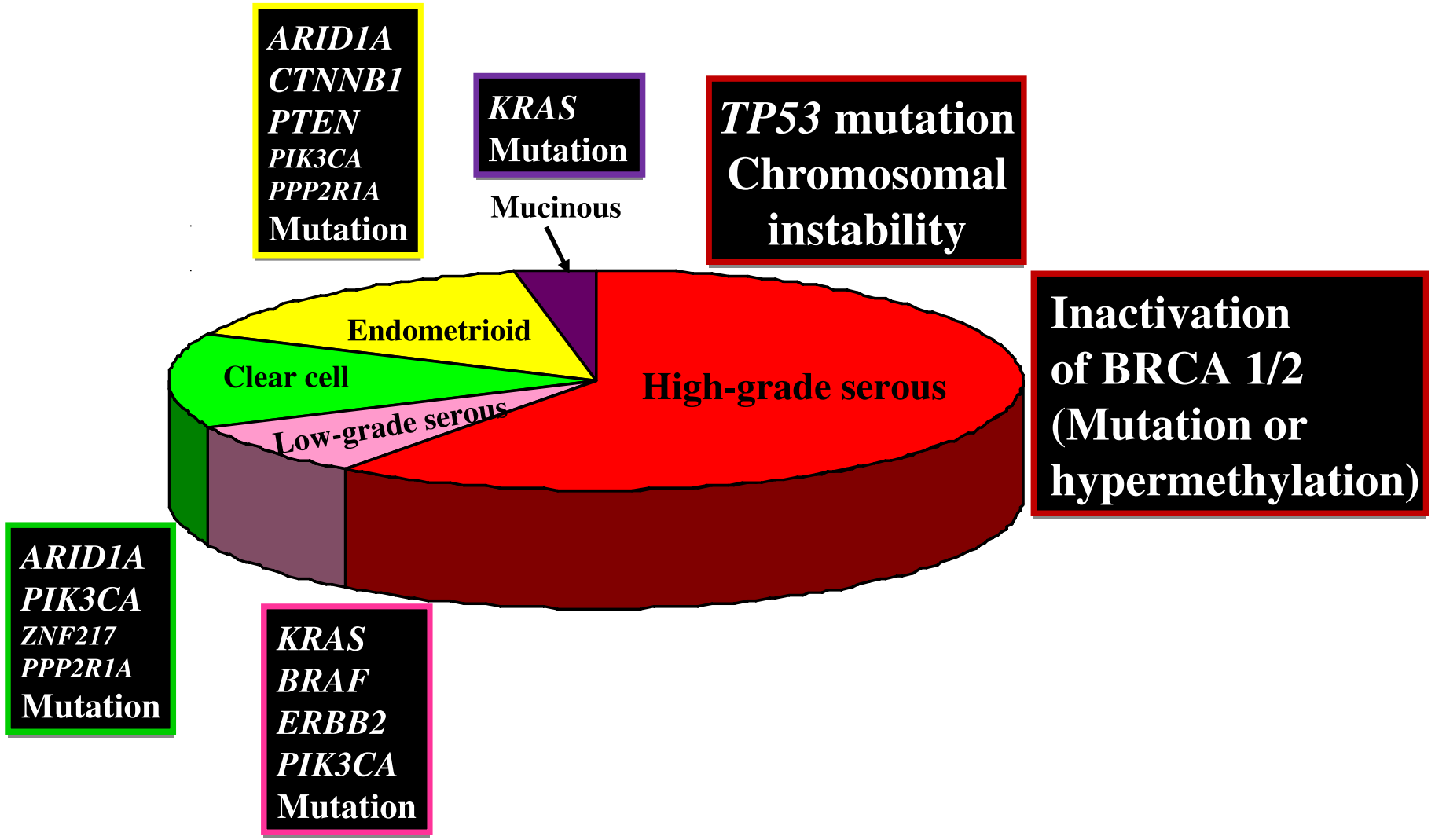
Outline

- Ovarian carcinoma classification
- High grade serous carcinoma
- Low grade serous carcinoma
- Carcinosarcoma
- Where next?

Classification of Ovarian Epithelial Tumours





Kurman and Shih Hum Pathol 2011; 42: 918-931

Diagnostic Biomarkers and Beyond

ORIGINAL ARTICLE

Diagnosis of Ovarian Carcinoma Cell Type is Highly Reproducible

A Transcanadian Study

Martin Köbel, MD, Steve E. Kalloger, BSc,† Patricia M. Baker, MD,‡ Carol A. Ewanowich, MD,§ Jocelyne Arseneau, MD,‖ Viktor Zherebitskiy, MD,‡ Soran Abdulkarim, MD,¶ Samuel Leung, MSc,† Máire A. Duggan, MD,* Dan Fontaine, MD,¶ Robin Parker, MD,# David G. Huntsman, MD,† and C. Blake Gilks, MD, FRCPC†*

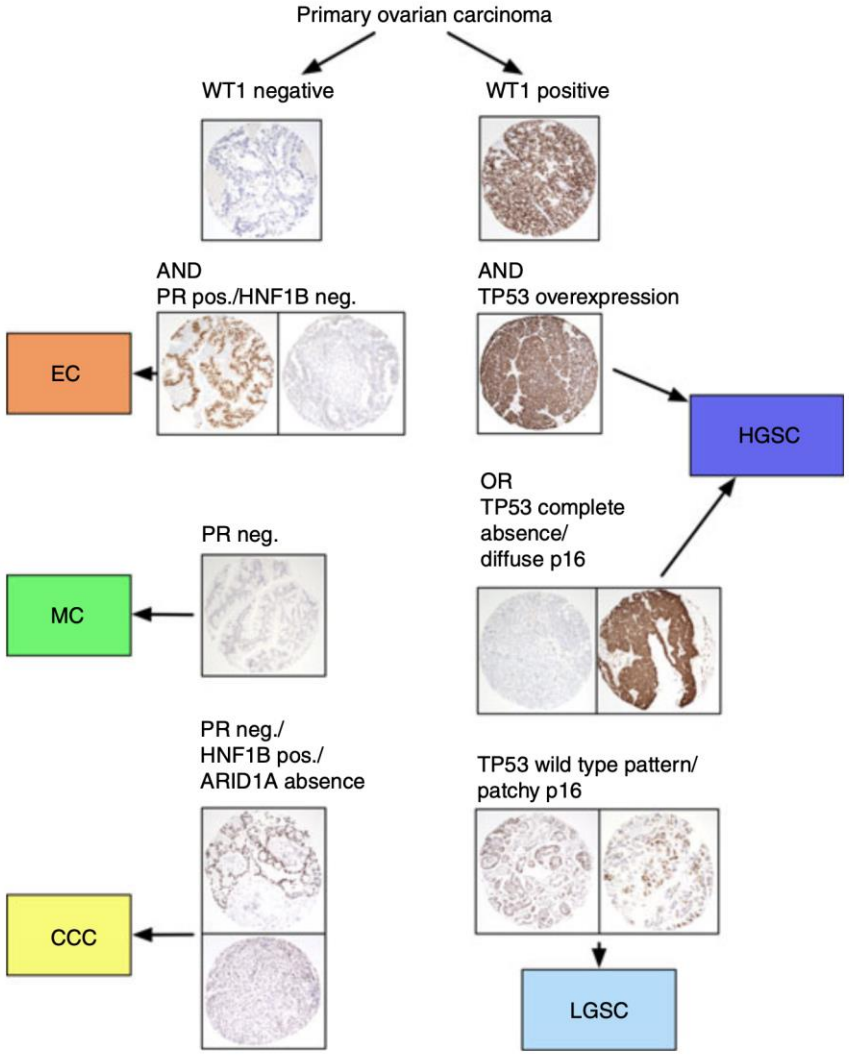
Am J Surg Pathol 2010; 34: 984-993

Histopathology

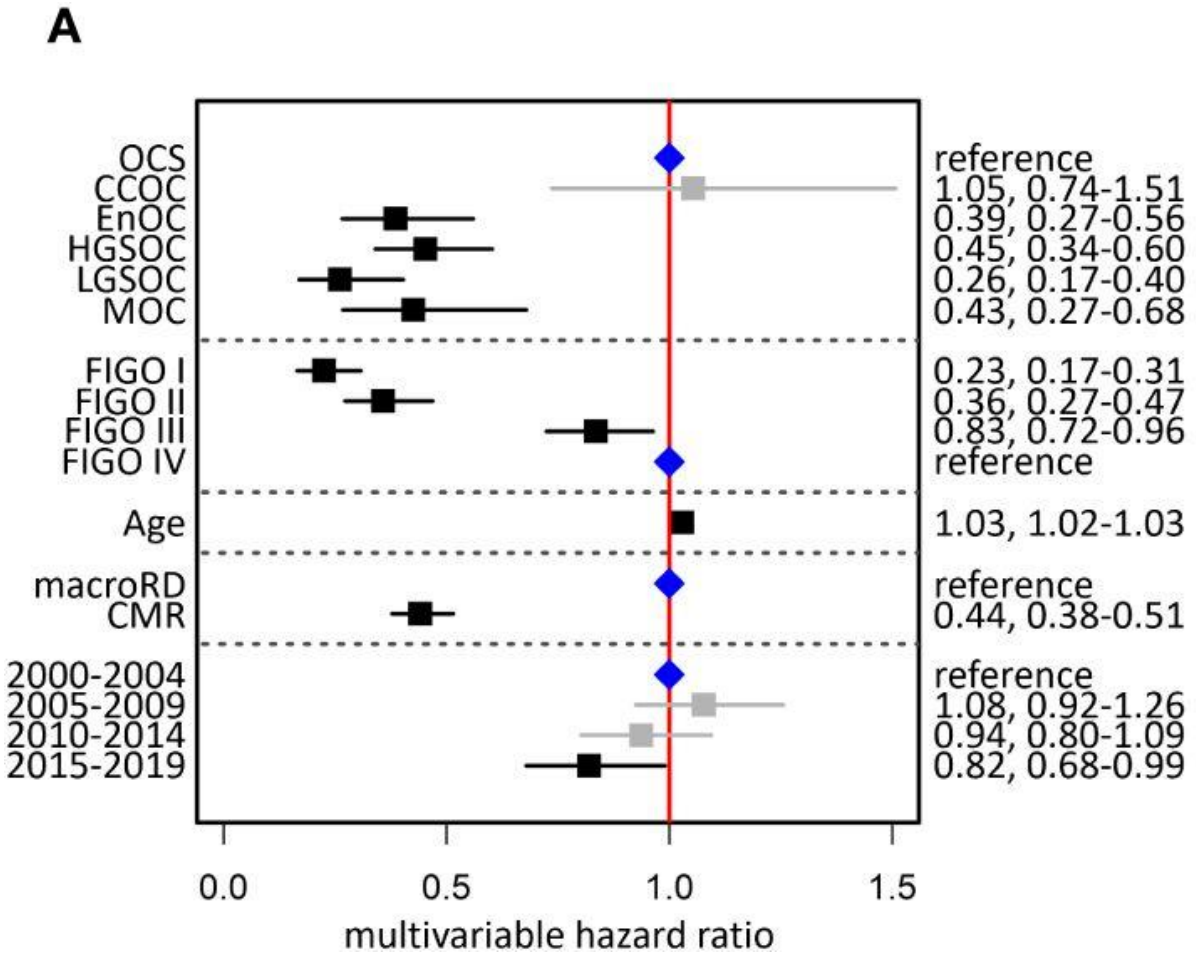
Histopathology 2014, **64**, 1004–1013. DOI: 10.1111/his.12349

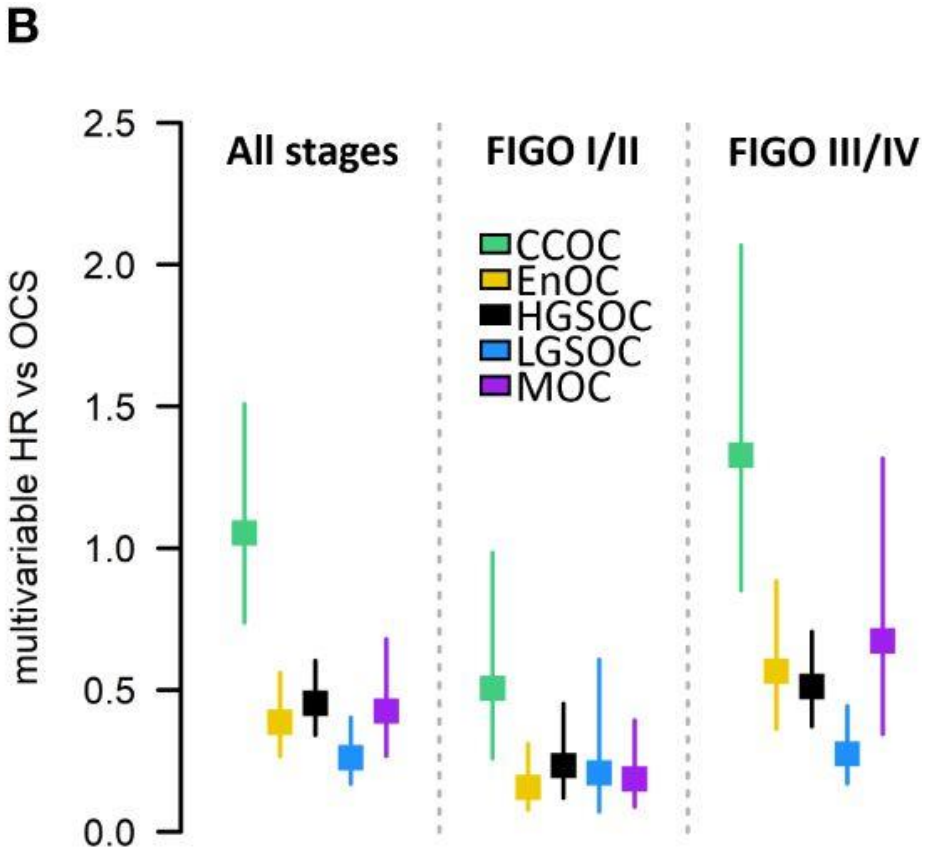
Ovarian carcinoma histotype determination is highly reproducible, and is improved through the use of immunohistochemistry

Martin Köbel, Julia Bak,[1] Björn I Bertelsen,[2] Olli Carpen,[3] Anni Grove,[4] Estrid S Hansen,[5] Anne-Marie Levin Jakobsen,[6] Marianne Lidang,[7] Anna Måsbäck,[8] Anna Tolf,[9] C Blake Gilks[10] & Joseph W Carlson[11]



Histotype and Outcome

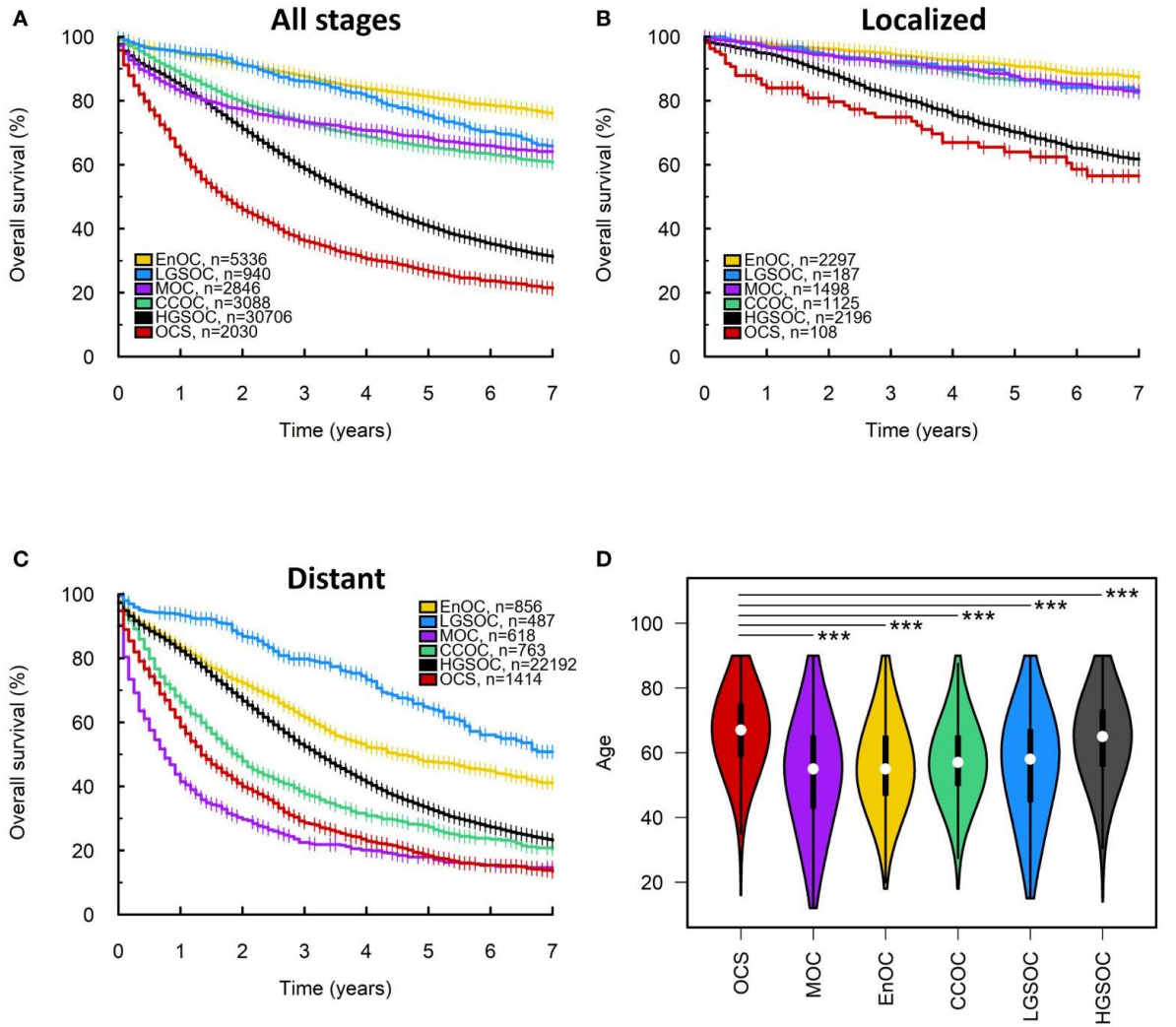


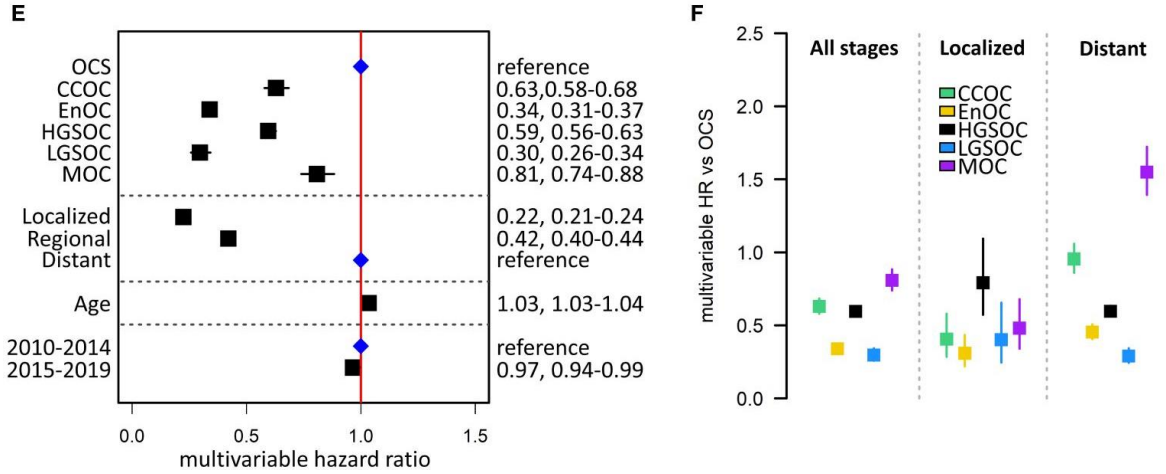


Scottish cohort, n = 2082

McFarlane et al, Front Oncol 2024; 14: 1399979

Histotype and Outcome





SEER cohort, n = 44946

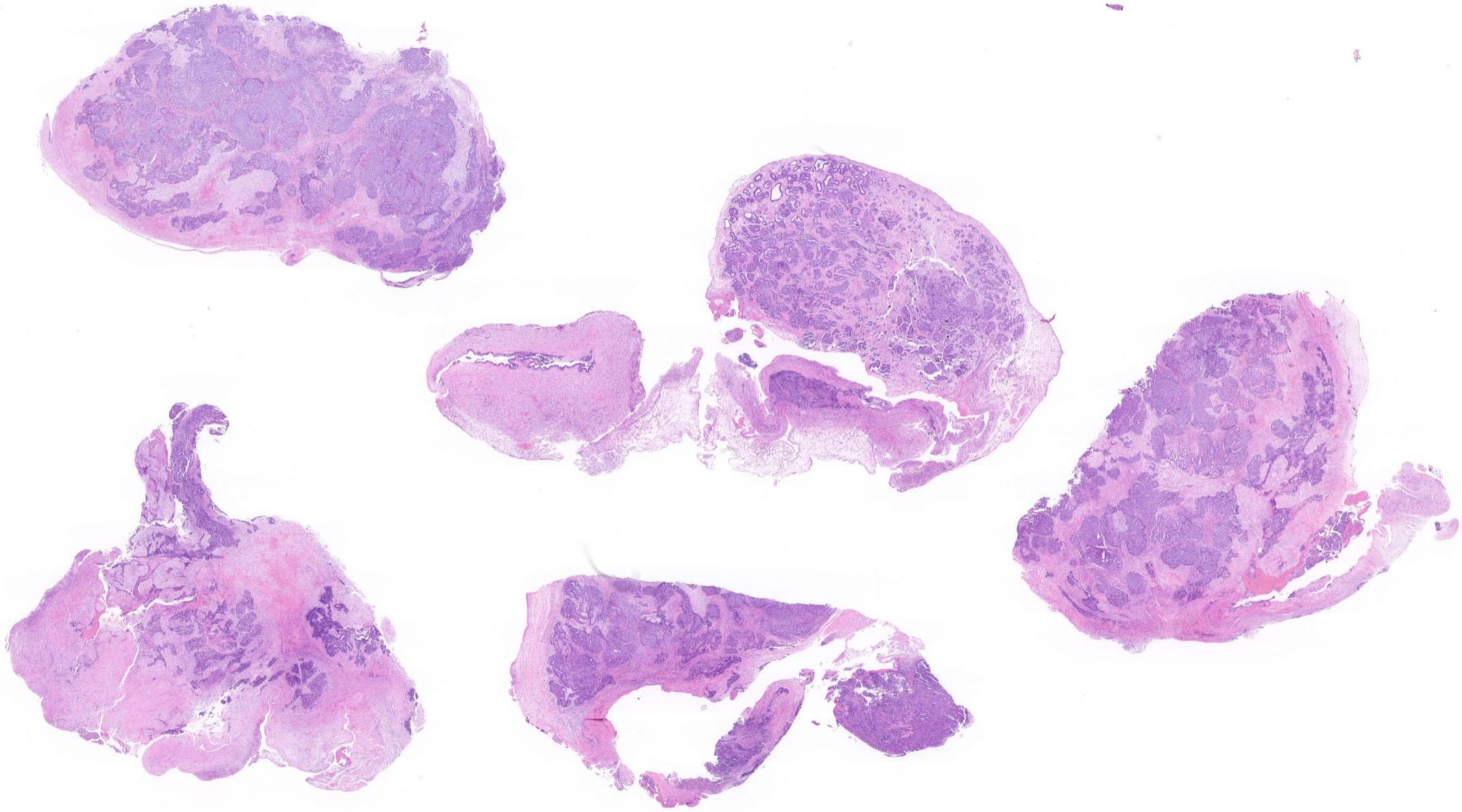
McFarlane et al, Front Oncol 2024; 14: 1399979

Outline

- Ovarian carcinoma classification
- High grade serous carcinoma
- Low grade serous carcinoma
- Carcinosarcoma
- Where next?

Case

- Female aged 59
- Right iliac fossa pain
- Laparoscopy revealed ascites, large left ovarian mass, omental cake and possible peritoneal disease.
- Left ovarian biopsies and peritoneal fluid received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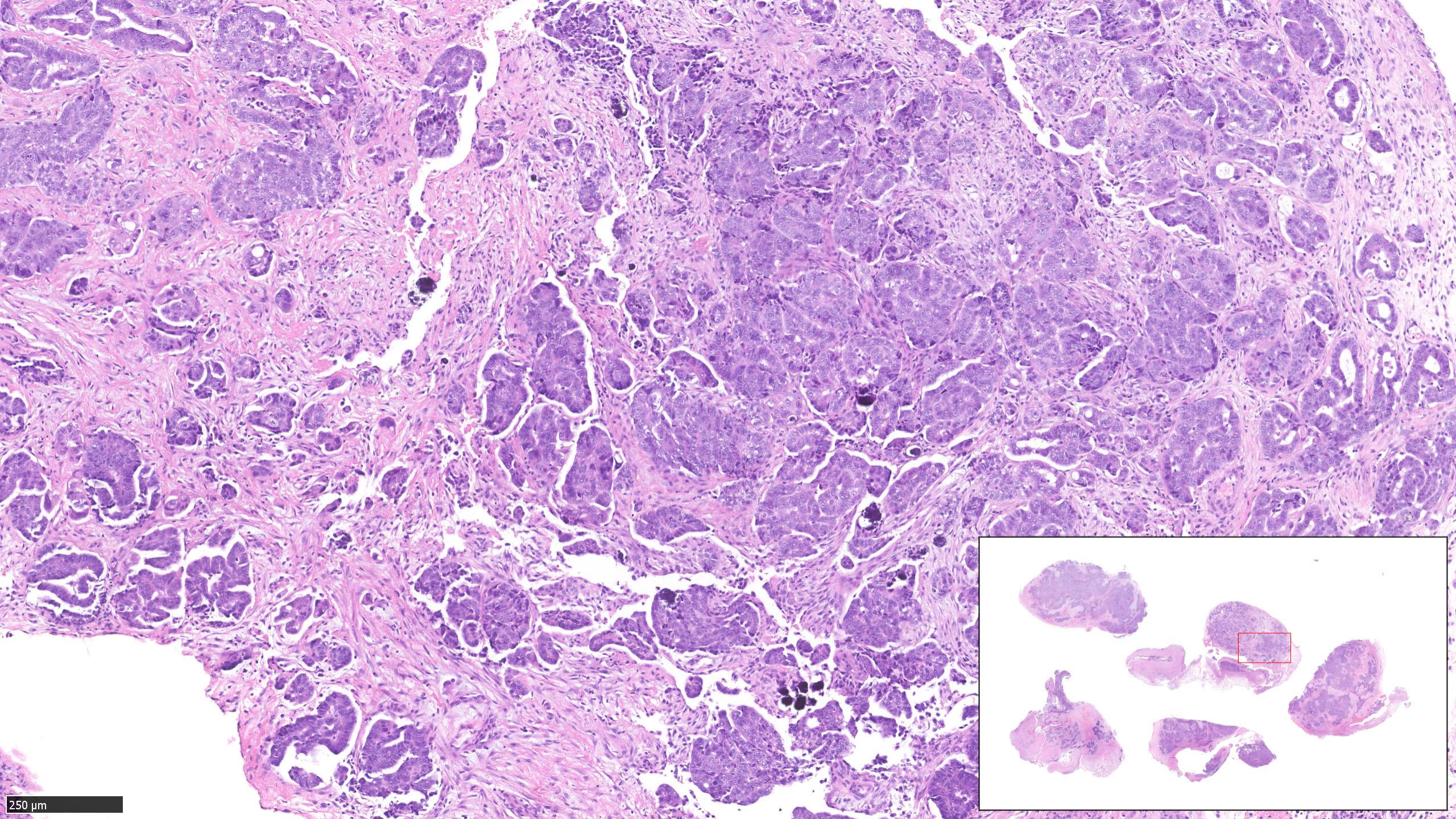
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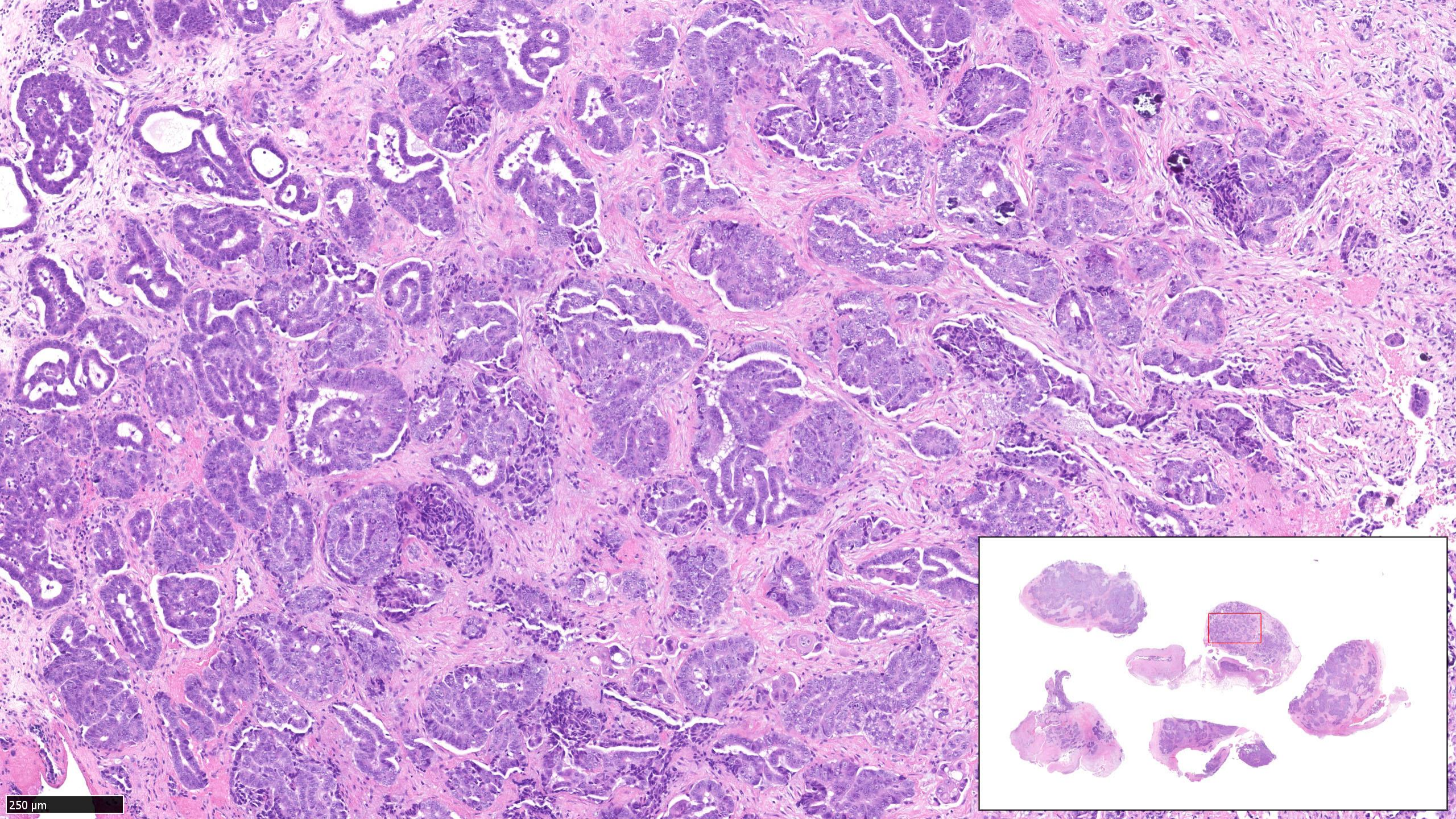
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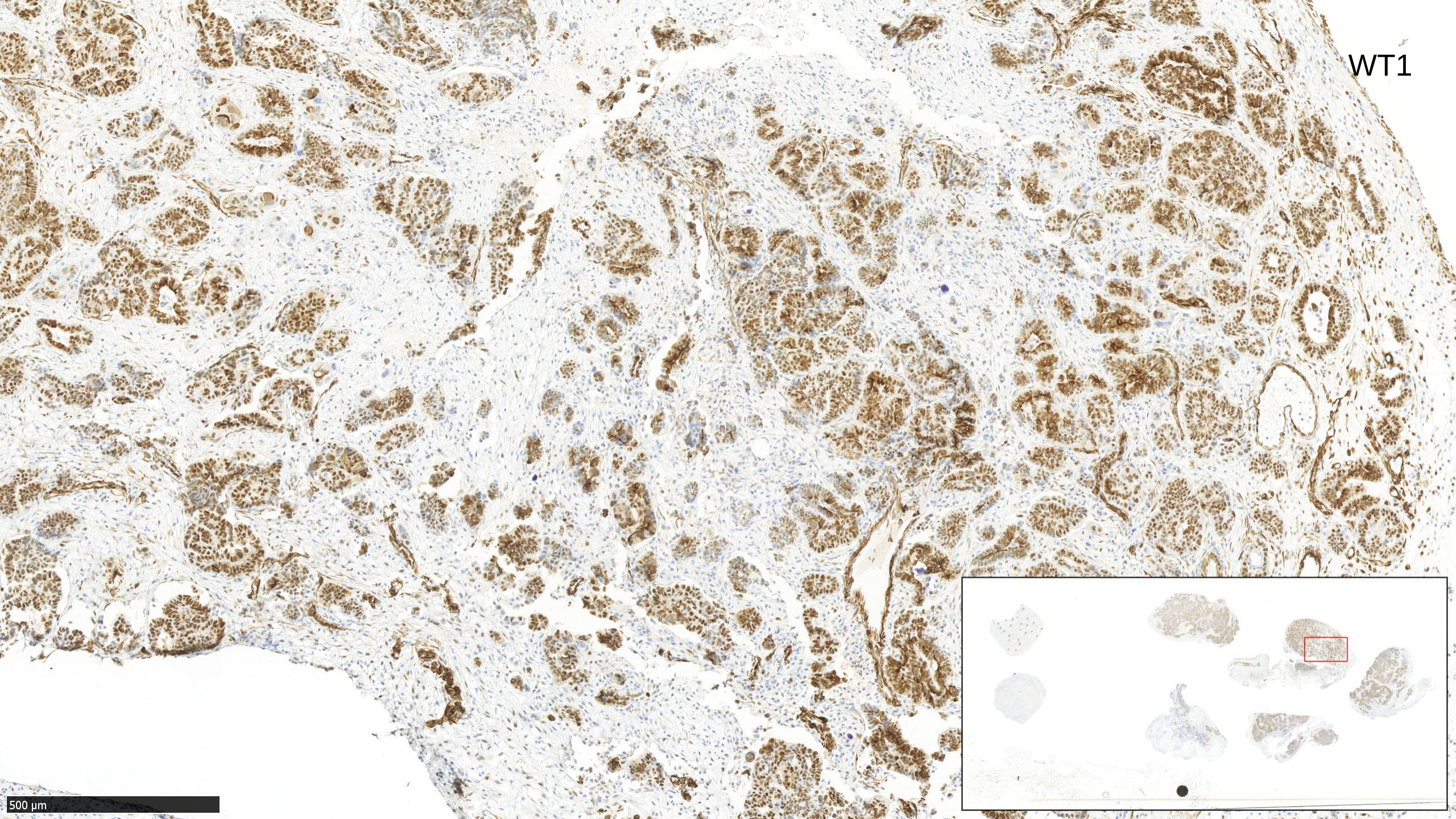
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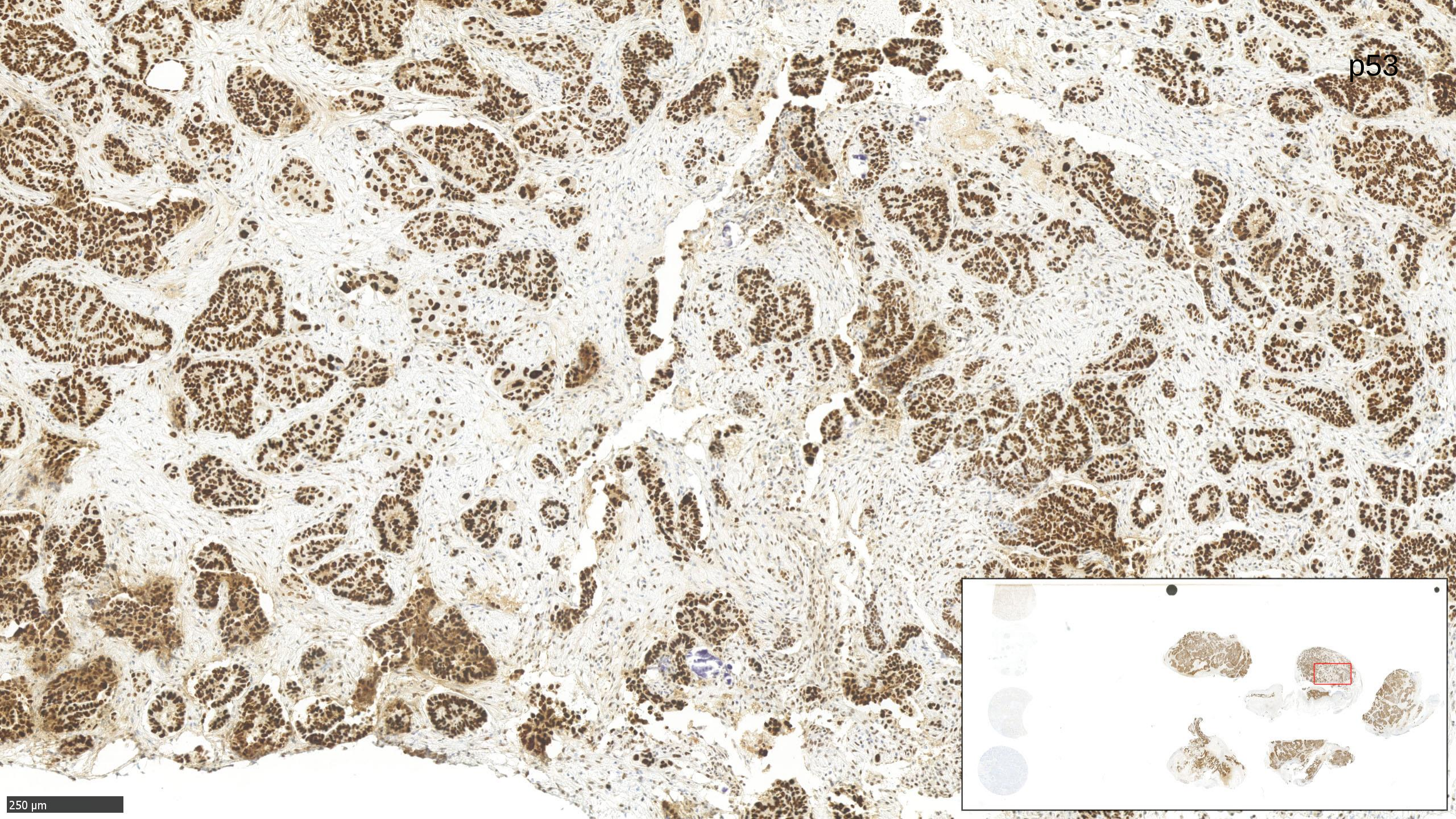
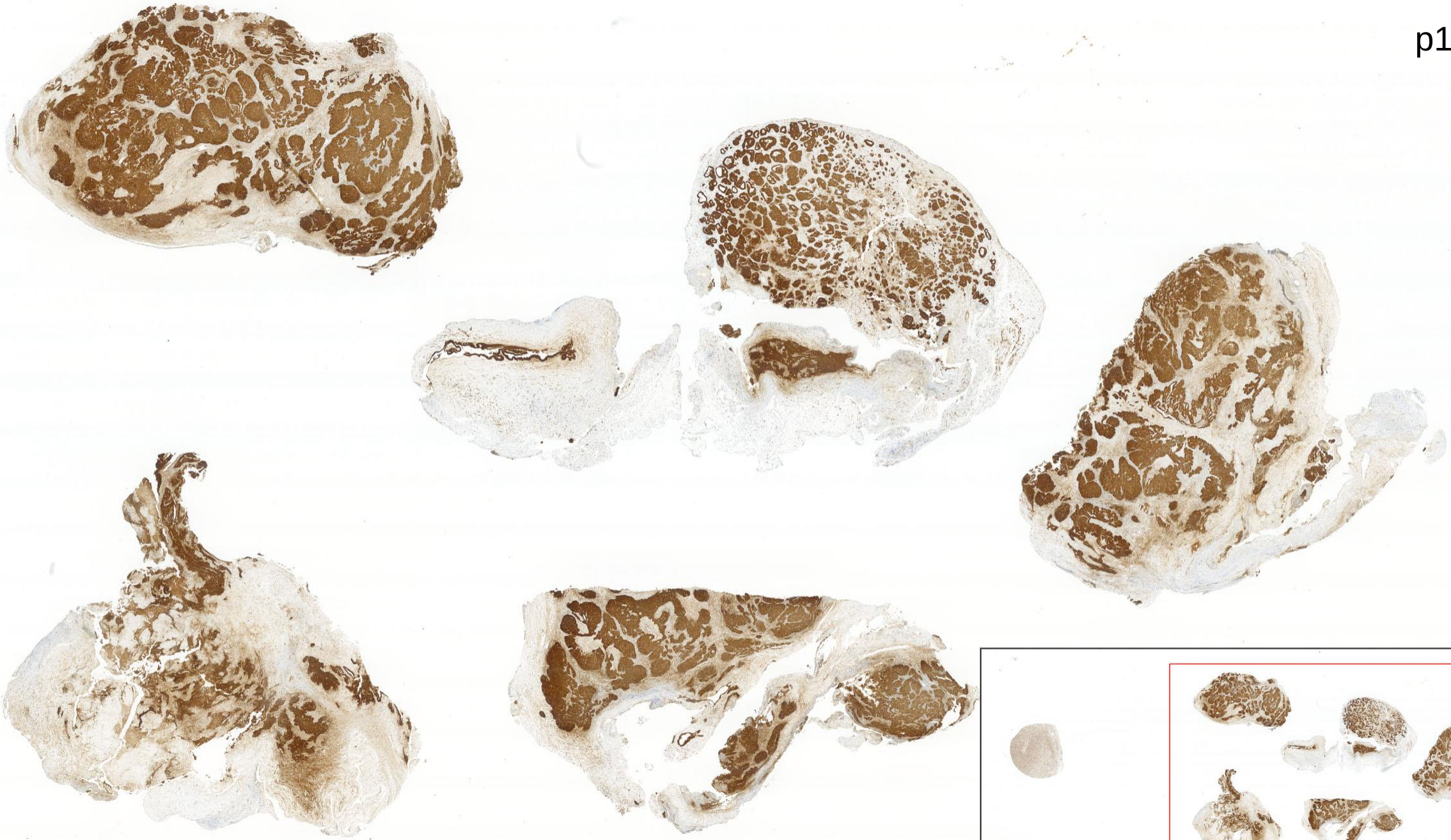
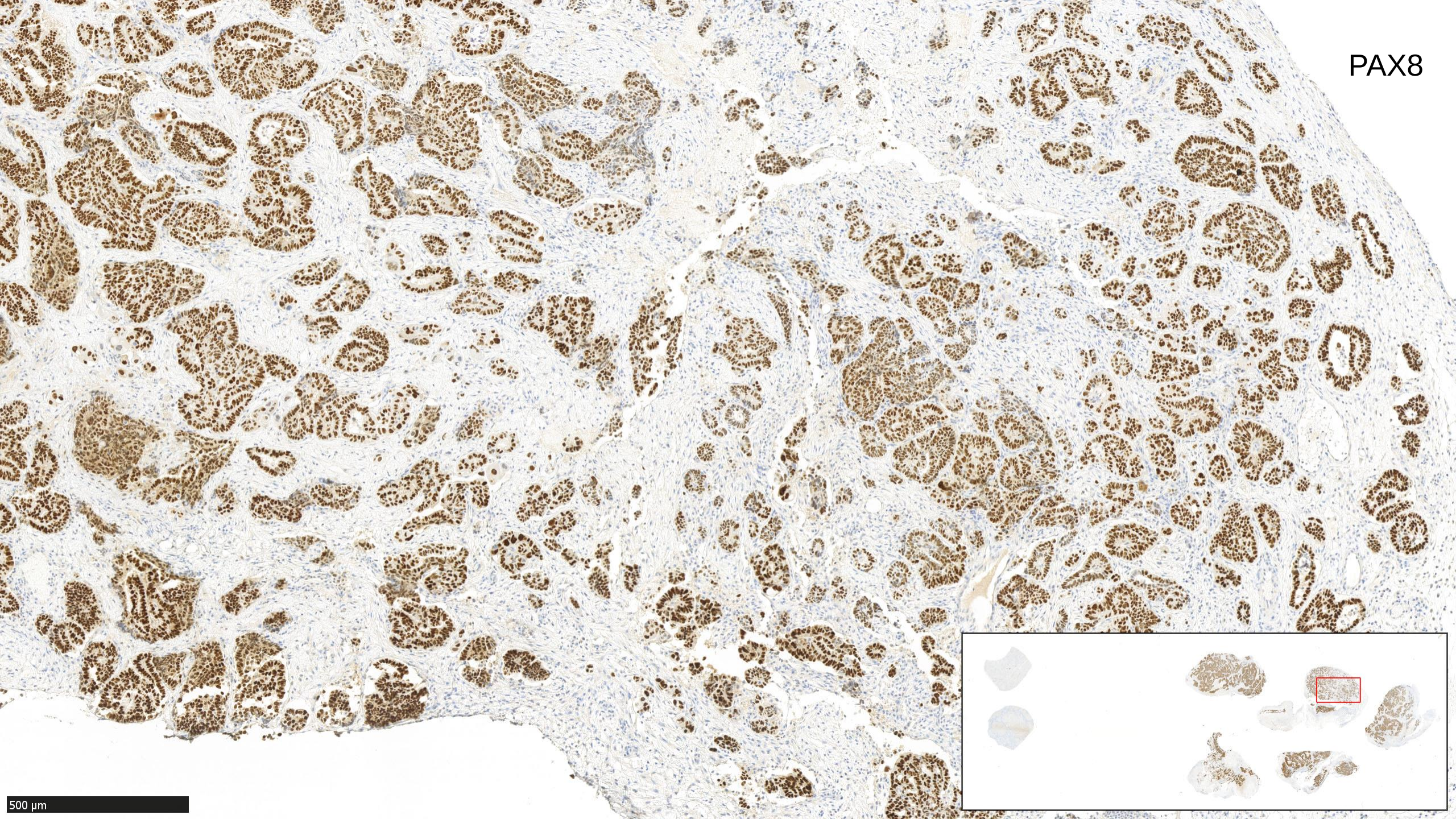

p53
250 µm

p16

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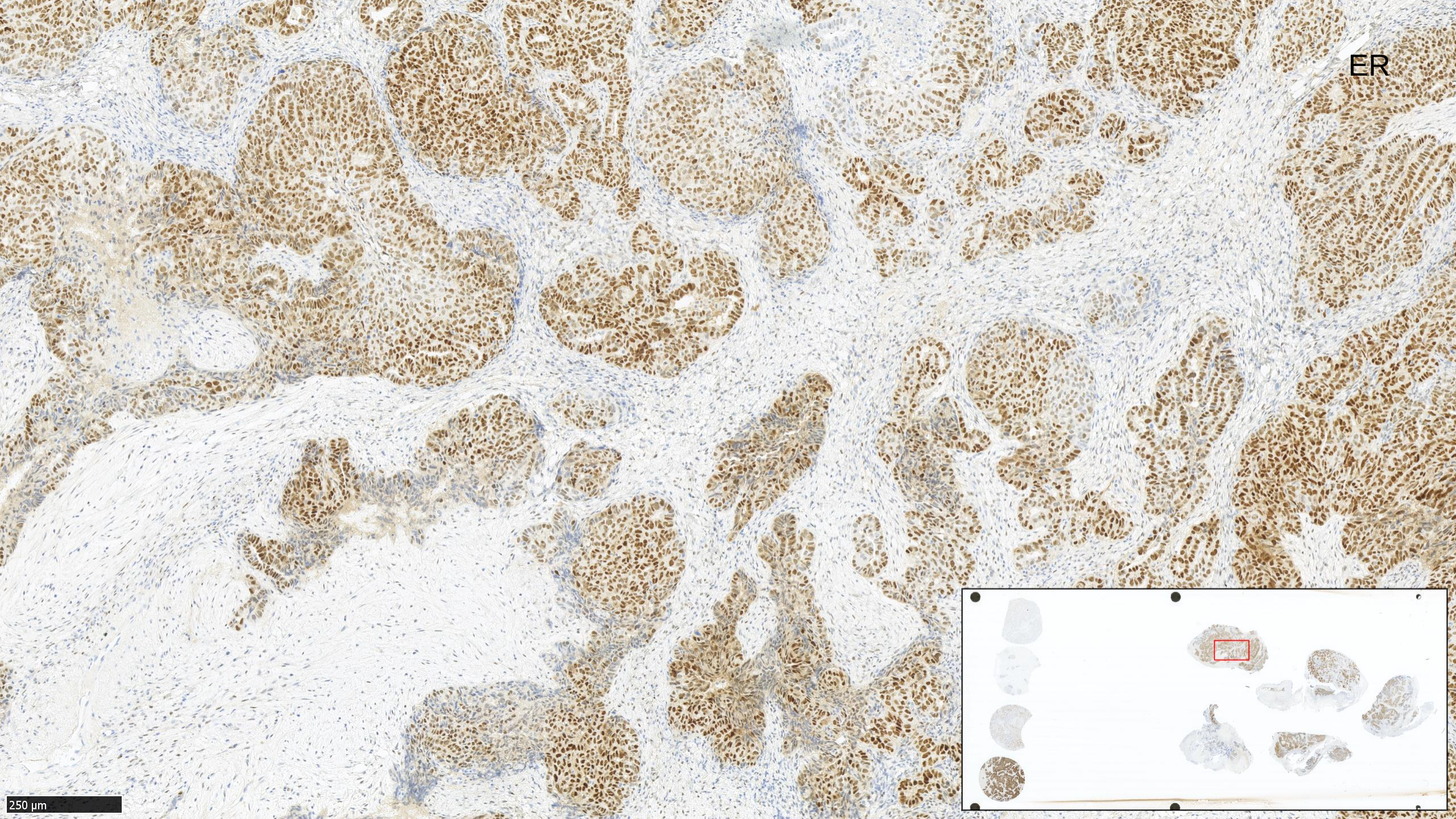
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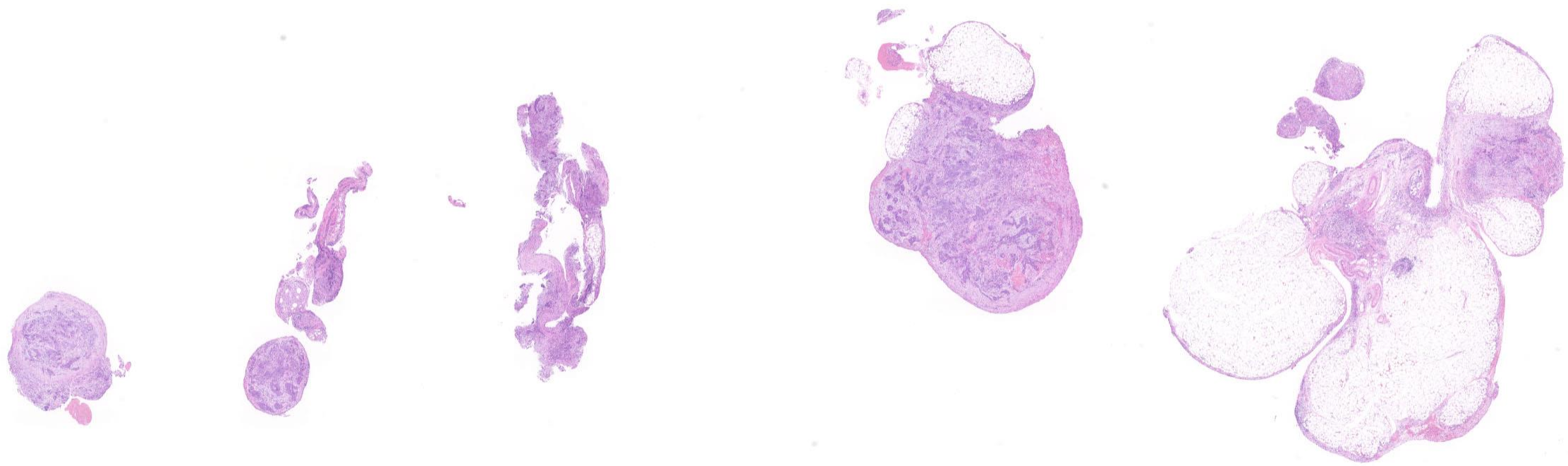
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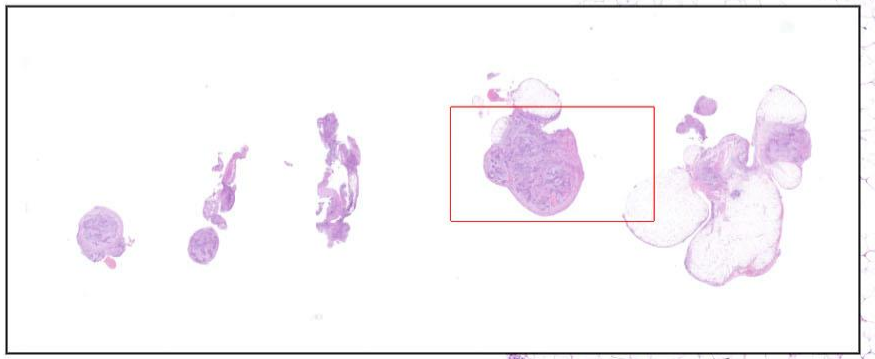

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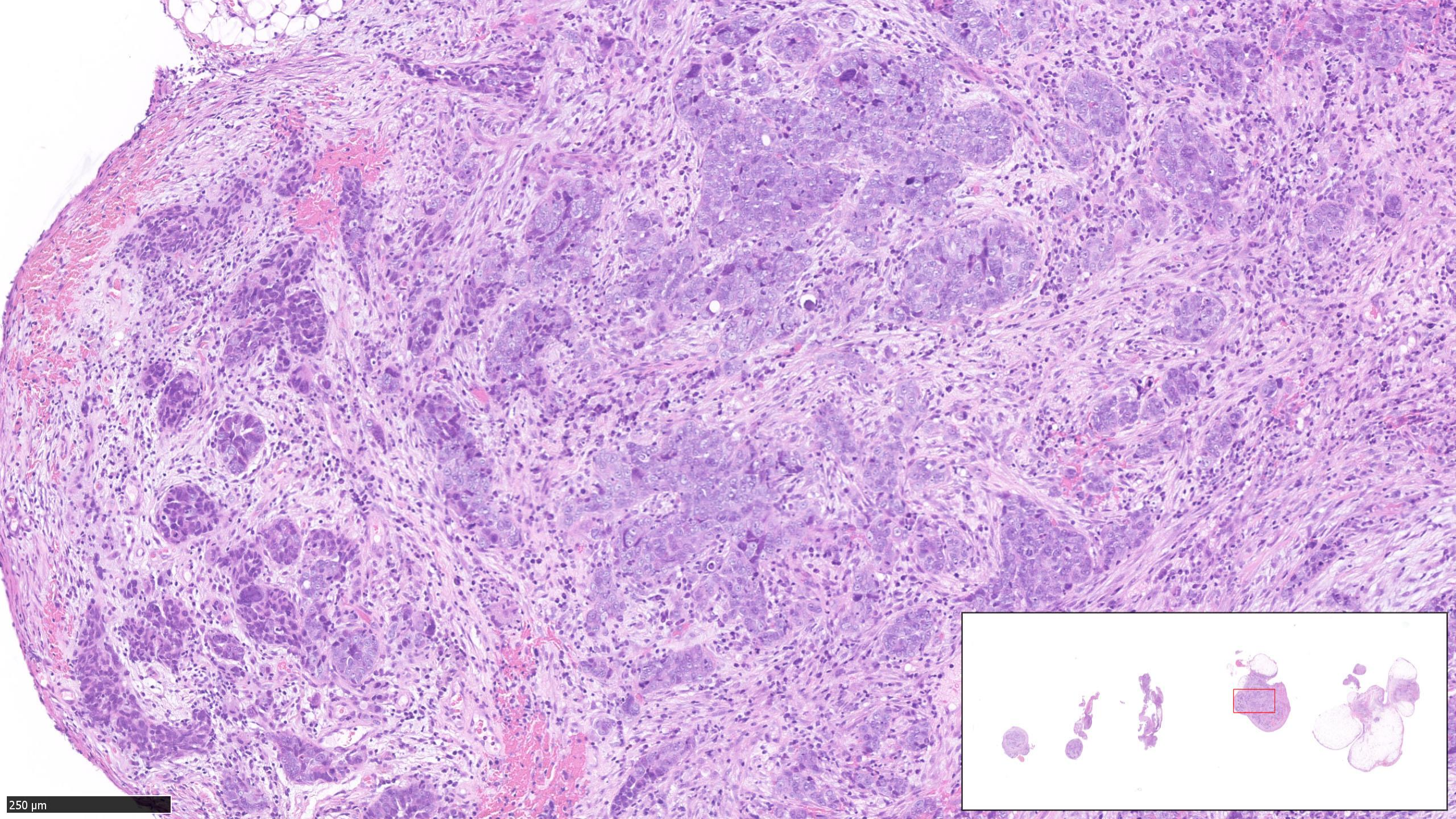
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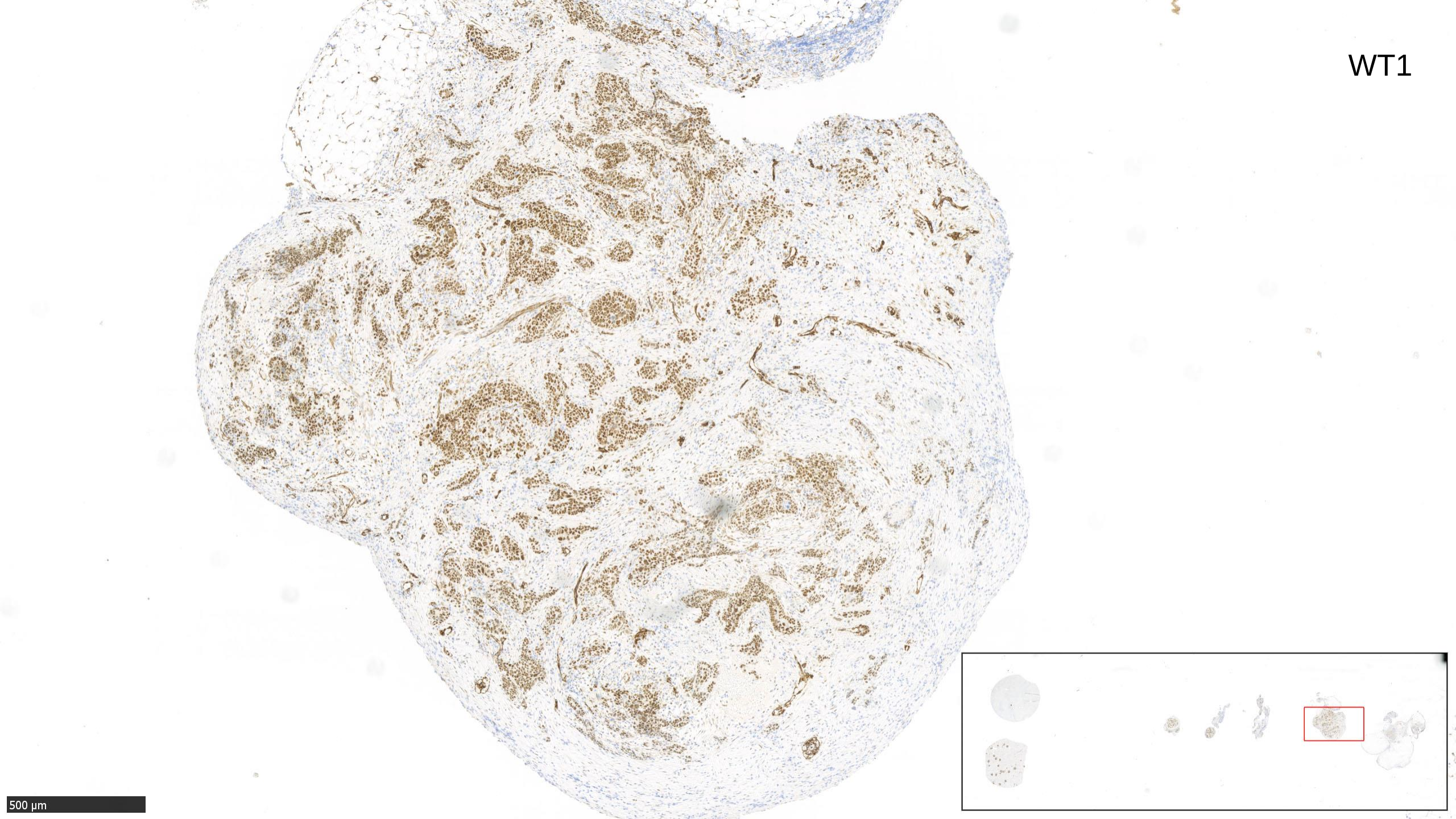
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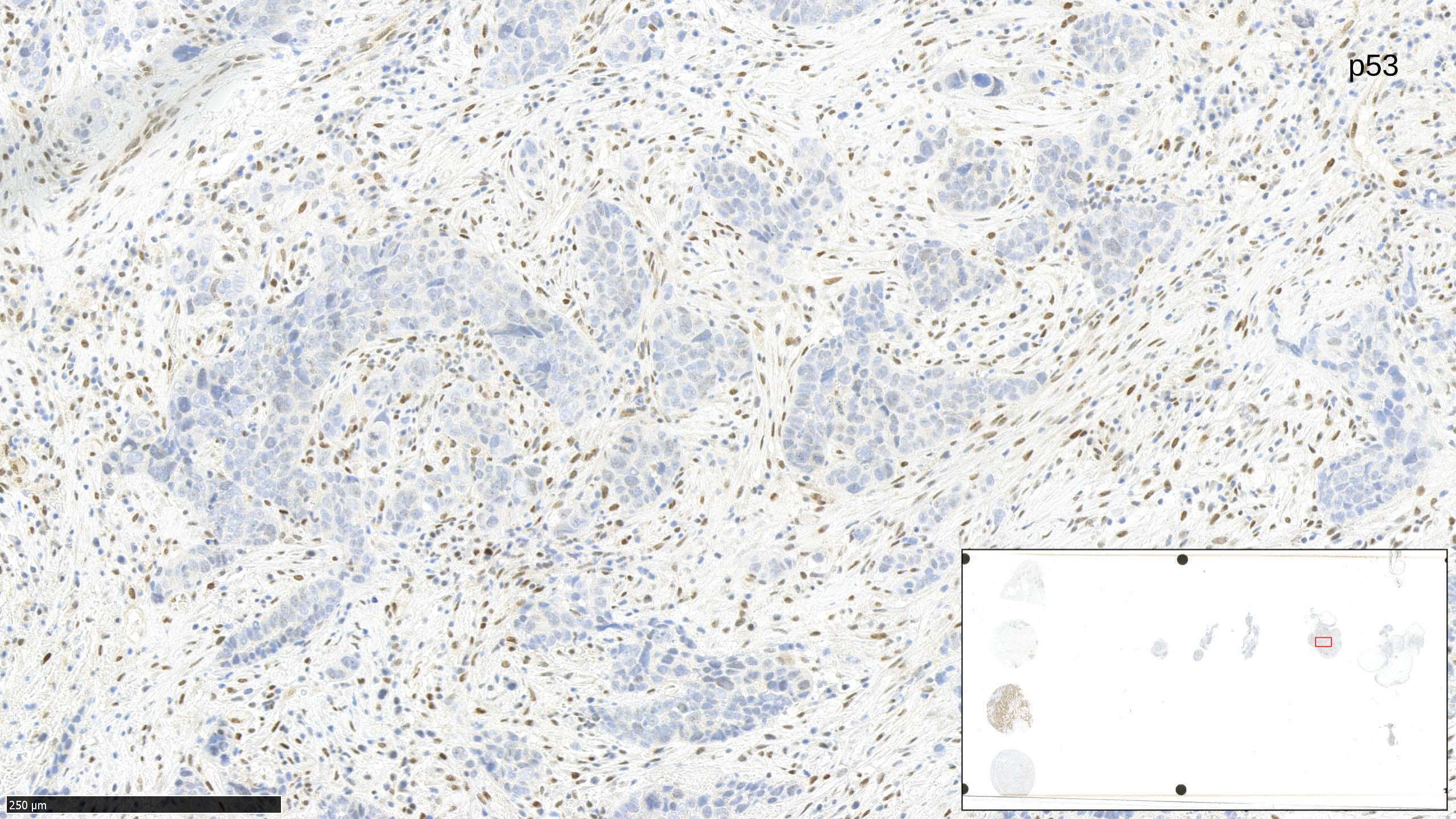
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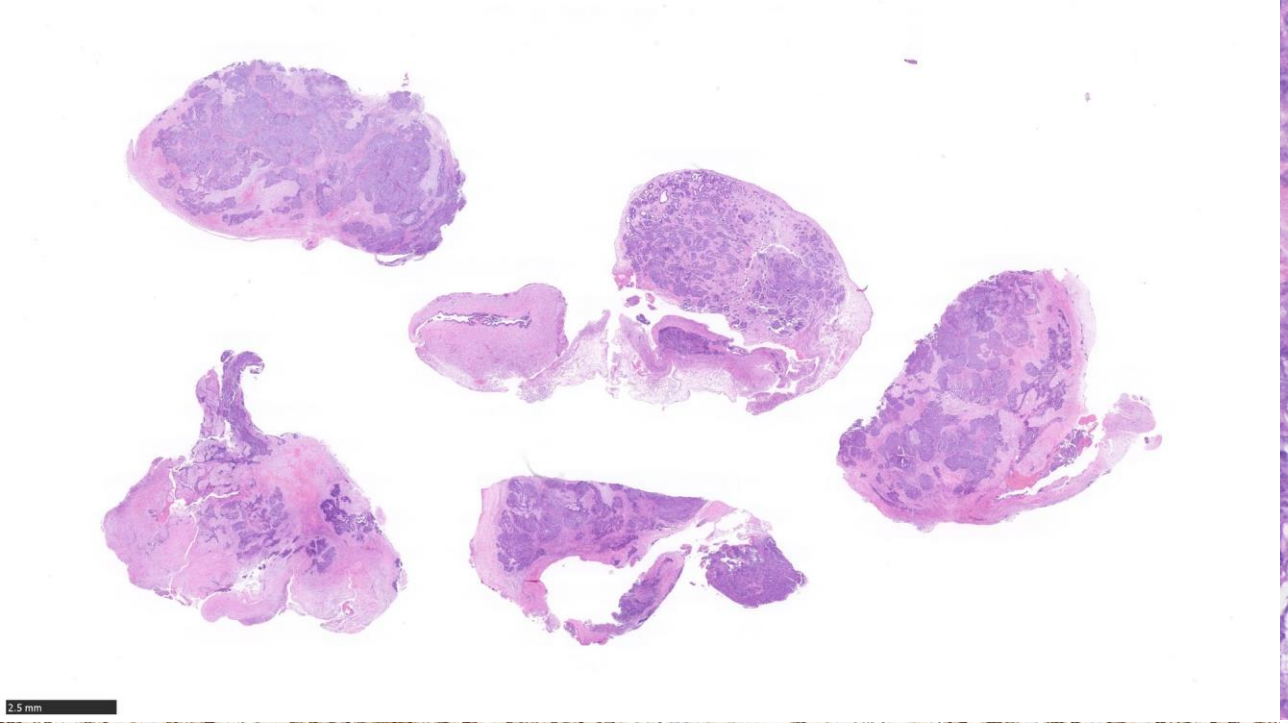
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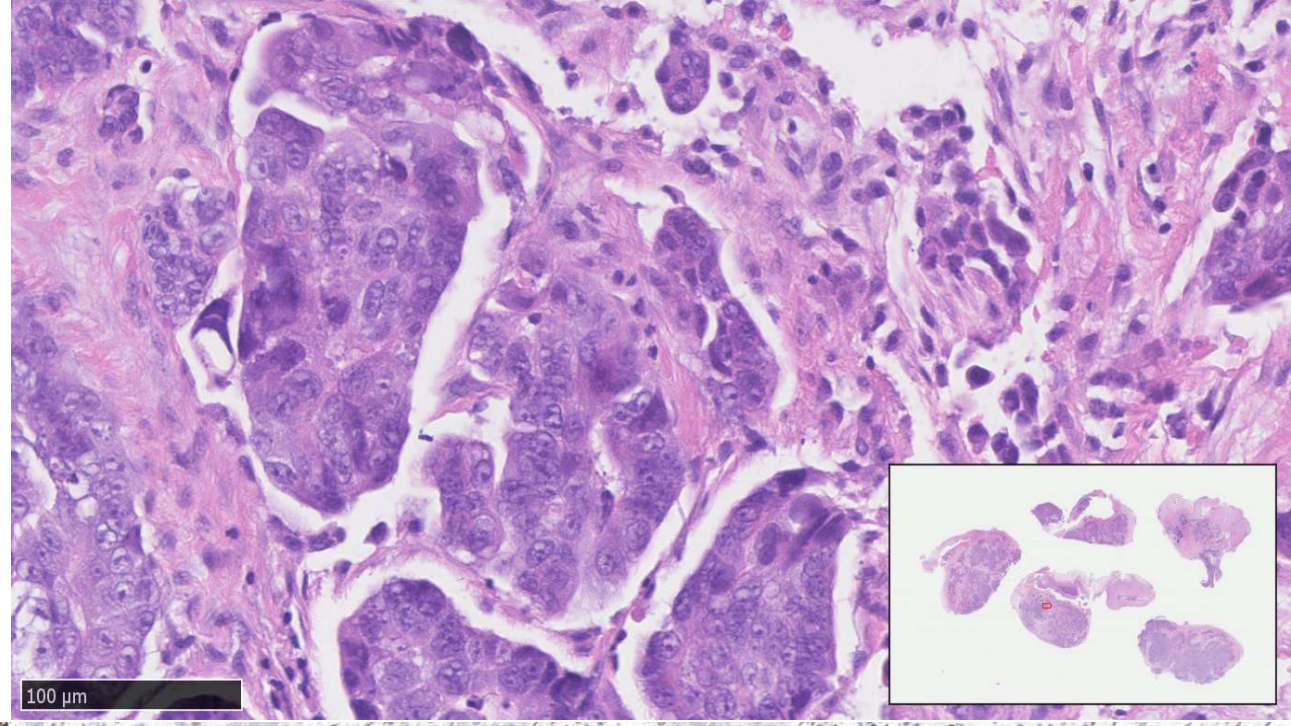
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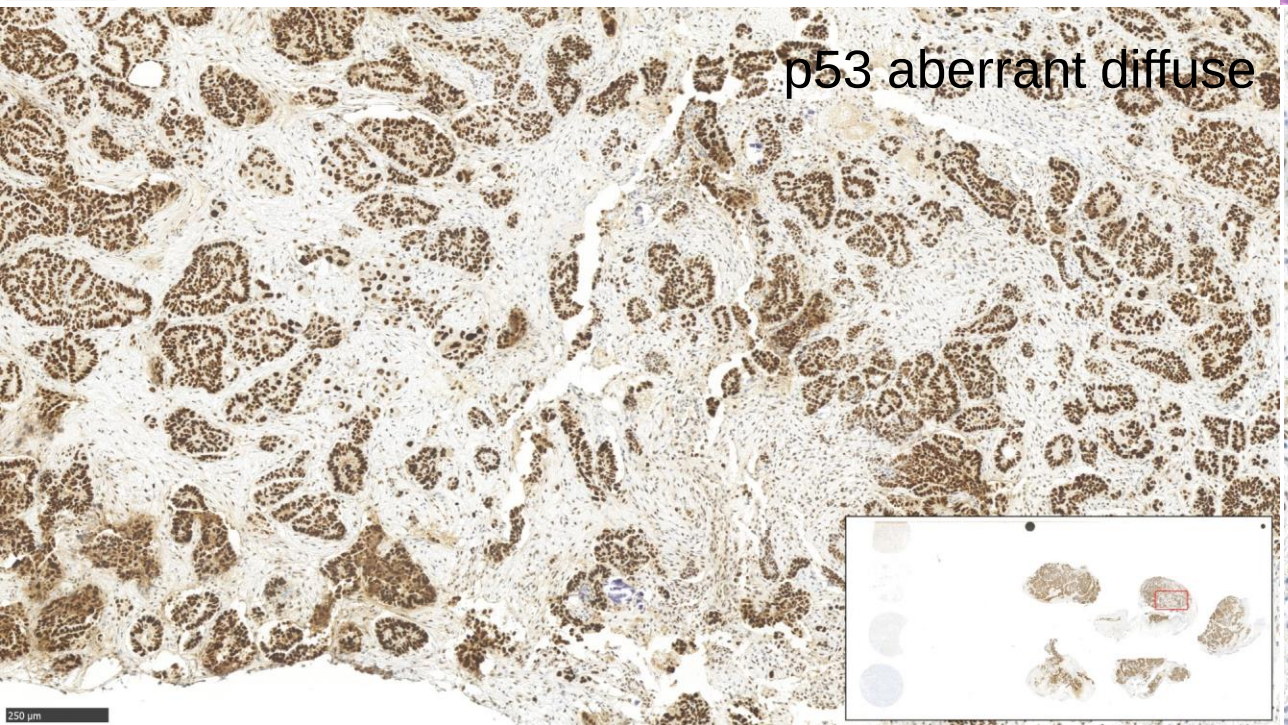
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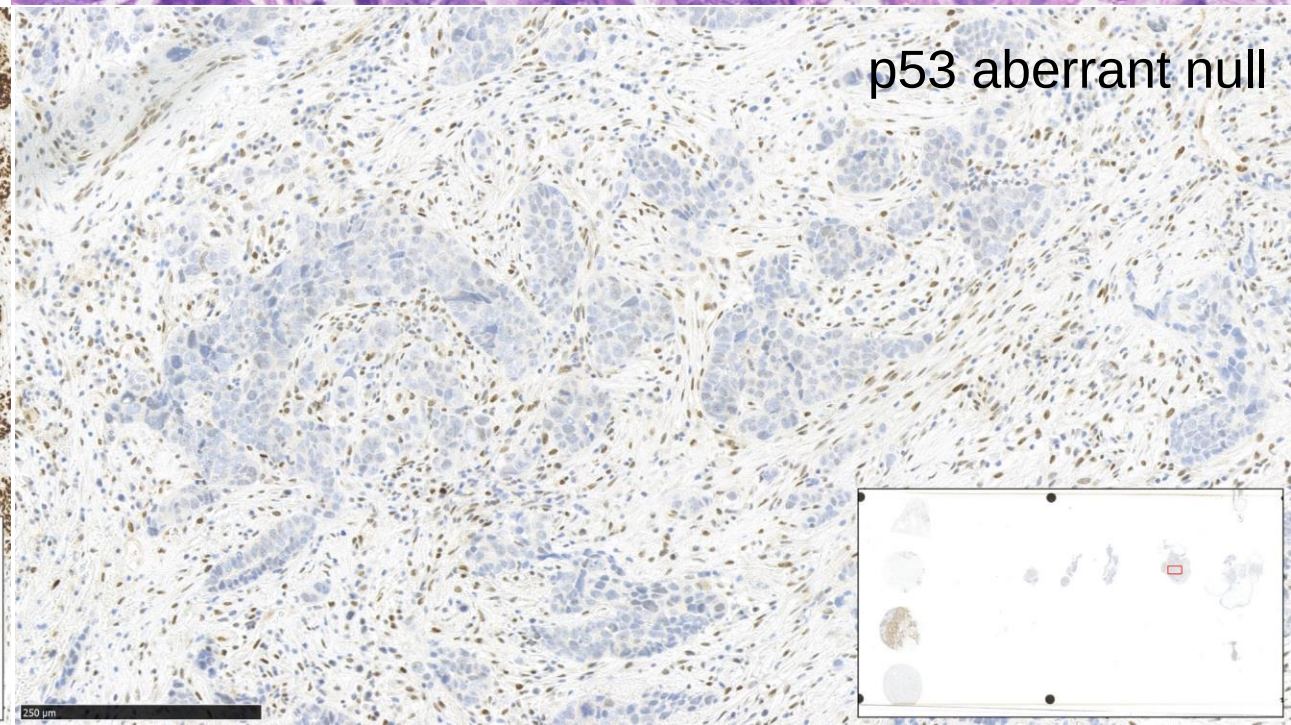
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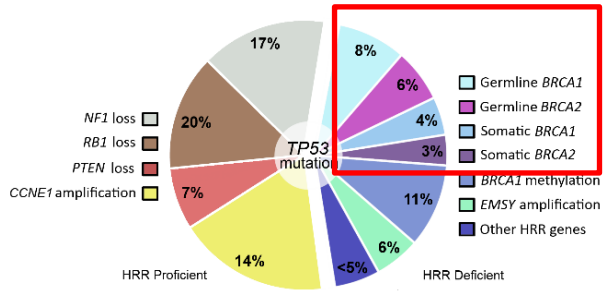
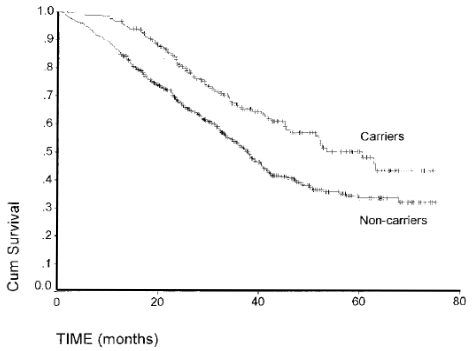
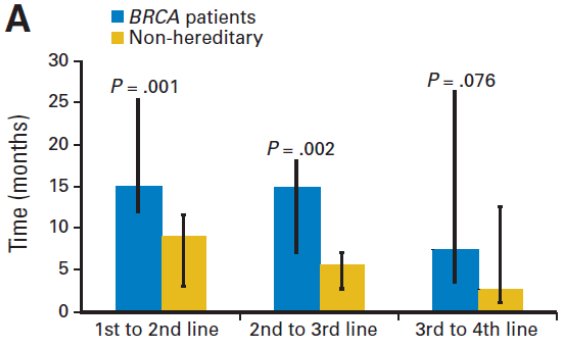
BRCA Mutant Ovarian Carcinoma - "BRCAness"

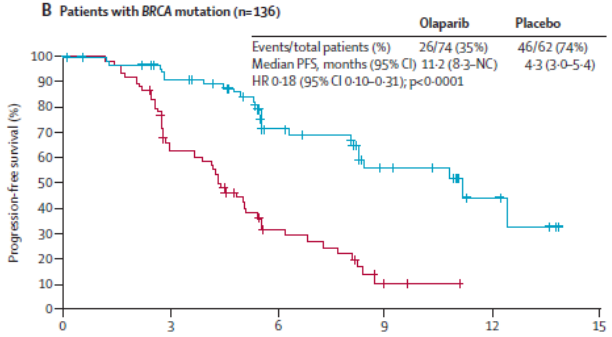




- Superior survival



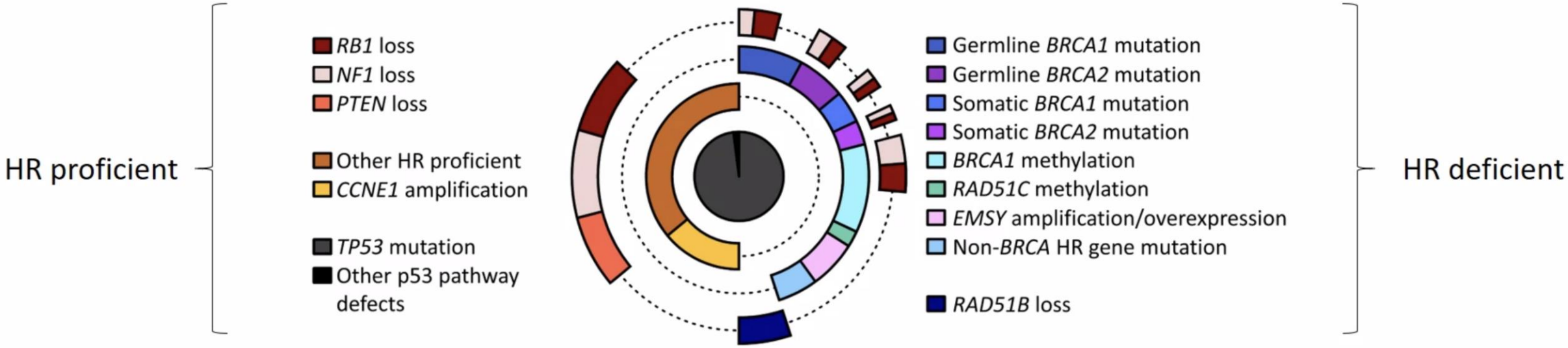
- Superior response rate to multiple lines of platinum and prolonged platinum-free interval



- Sensitivity to PARP inhibitors

Ben David Y et al. J Clin Oncol 2002;20:463-6.
Tan DS et al. J Clin Oncol 2008;26:5530-6.
Ledermann J et al. Lancet Oncol 2014;15:852-61.
Moore et al. N Engl J Med 2018; 379: 2495-2505
DiSilvestro et al. J Clin Oncol 2023; 41: 609-617

Genomic Features of High-grade Serous Ovarian Carcinoma



Courtesy of Robb Hollis

The Journal of Pathology: Clinical Research
J Pathol Clin Res November 2023; **9:** 442–448
Published online 28 July 2023 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/cjp2.336

BRIEF REPORT

RAD51 as a biomarker for homologous recombination deficiency in high-grade serous ovarian carcinoma: robustness and interobserver variability of the RAD51 test

Claire JH Kramer[1], Alba Llop-Guevara[2], Elisa Yaniz-Galende[3], Benedetta Pellegrino[4,5], Natalja T ter Haar[1], Andrea Herencia-Ropero[2], Nicoletta Campanini[4,5], Antonino Musolino[4,5], Tjalling Bosse[1], Alexandra Leary[3], Violeta Serra[2] and Maaike PG Vreeswijk[6*]

TP53 wild-type high grade serous carcinoma?
Pathobiology uncertain

Chui MH et al, Mod Pathol 2021; 34:490-501

Outline

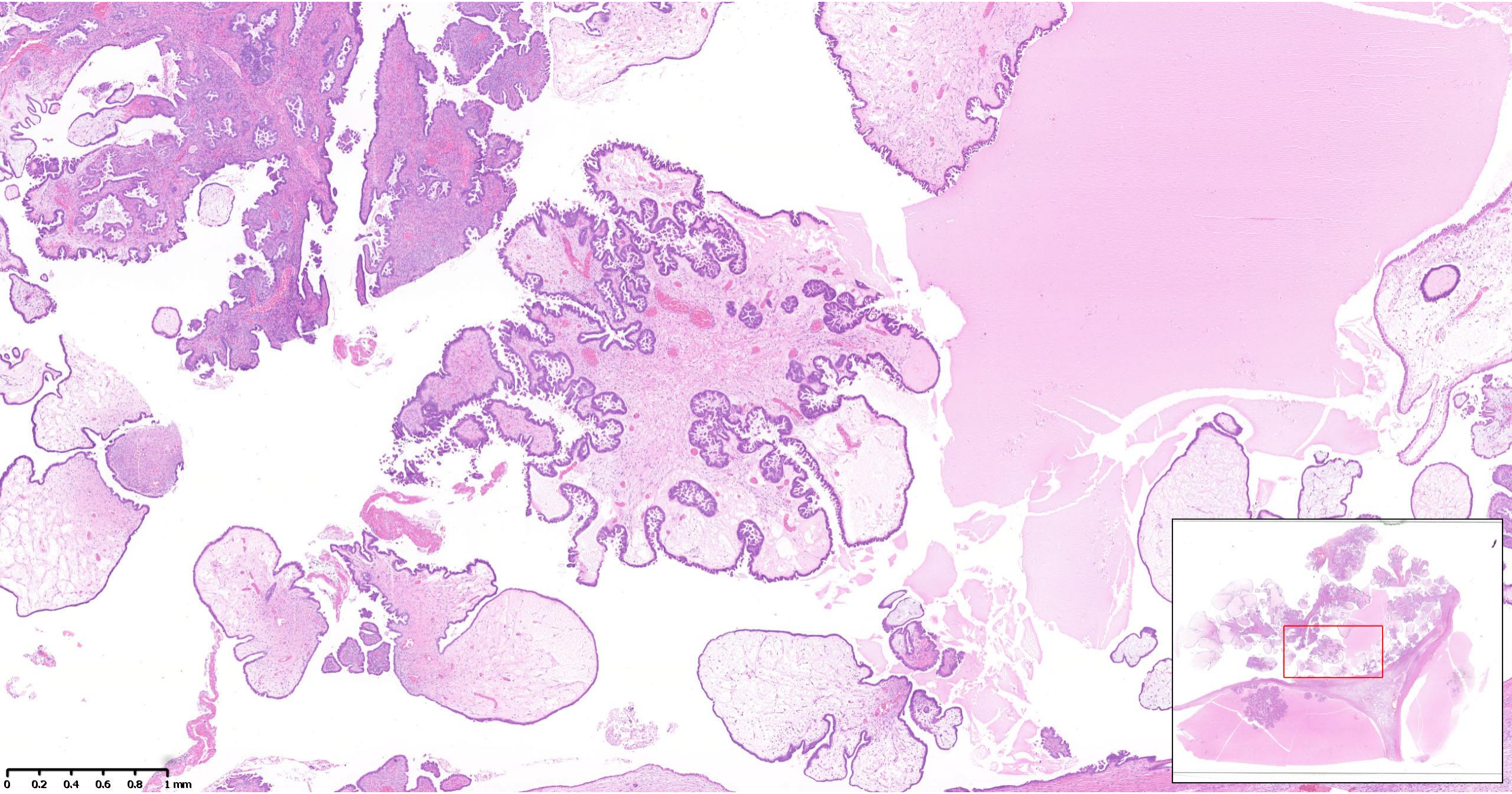
- Ovarian carcinoma classification
- High grade serous carcinoma
- Low grade serous carcinoma
- Carcinosarcoma
- Where next?

Low Grade Serous Carcinoma

- Associated with serous borderline tumours, which may show a micropapillary growth pattern
- Implants are by definition non-invasive and may be desmoplastic or non-desmoplastic
- Invasive deposits should be termed low grade serous carcinoma

Case

- Female aged 45
- Emergency admission with abdominal pain
- CT suggested dermoid cyst
- At laparotomy, disease involving uterus and colon
- Received TAH, BSO, omentum, sigmoid colon, peritoneal biopsy and washings
- Bilateral cystic ovarian masses 140 x 90 x 70 and 85 x 80 x 50 mm with surface papillary excrescences
- Sections from right ovarian tumour and uterine serosa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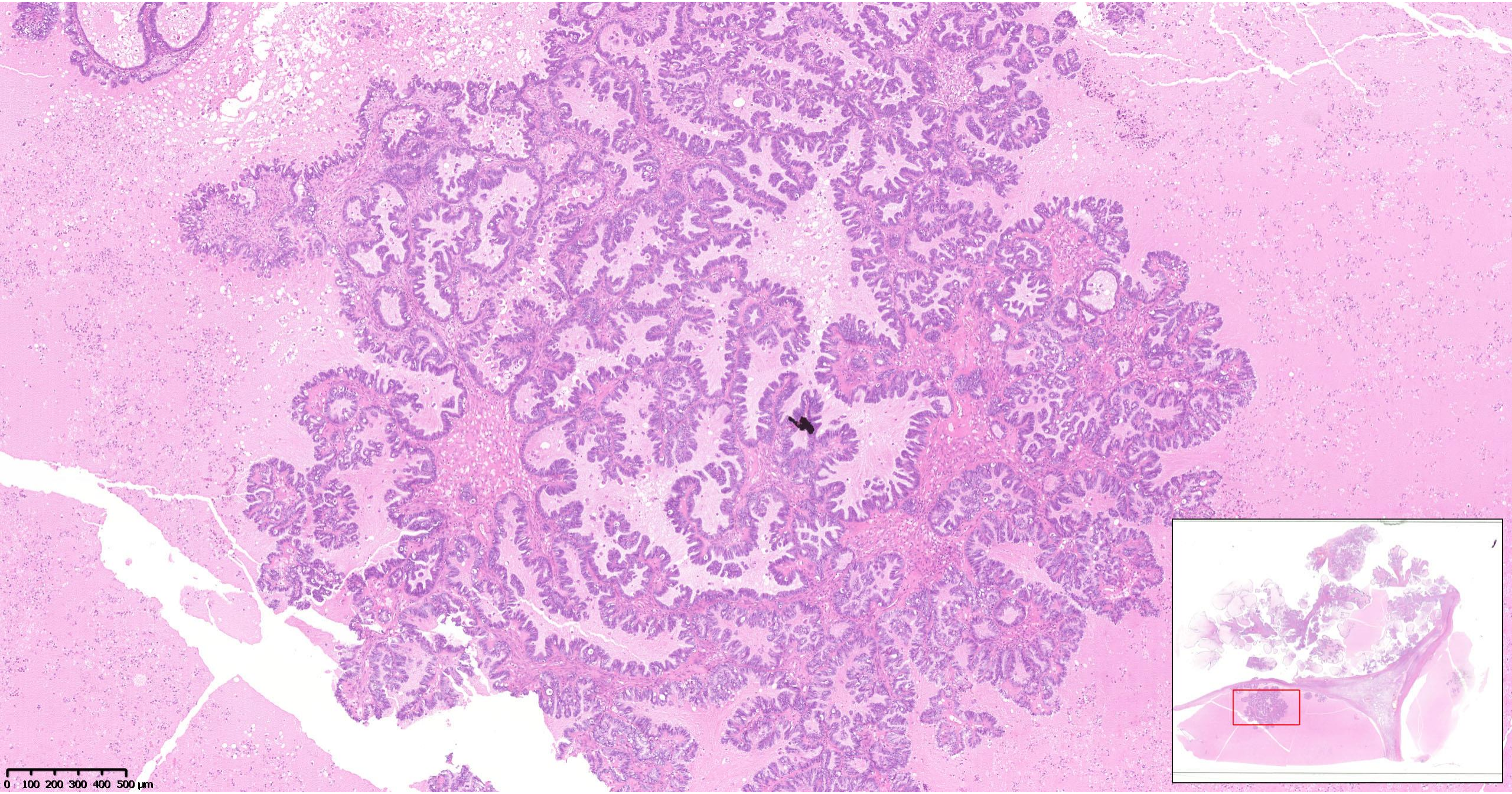
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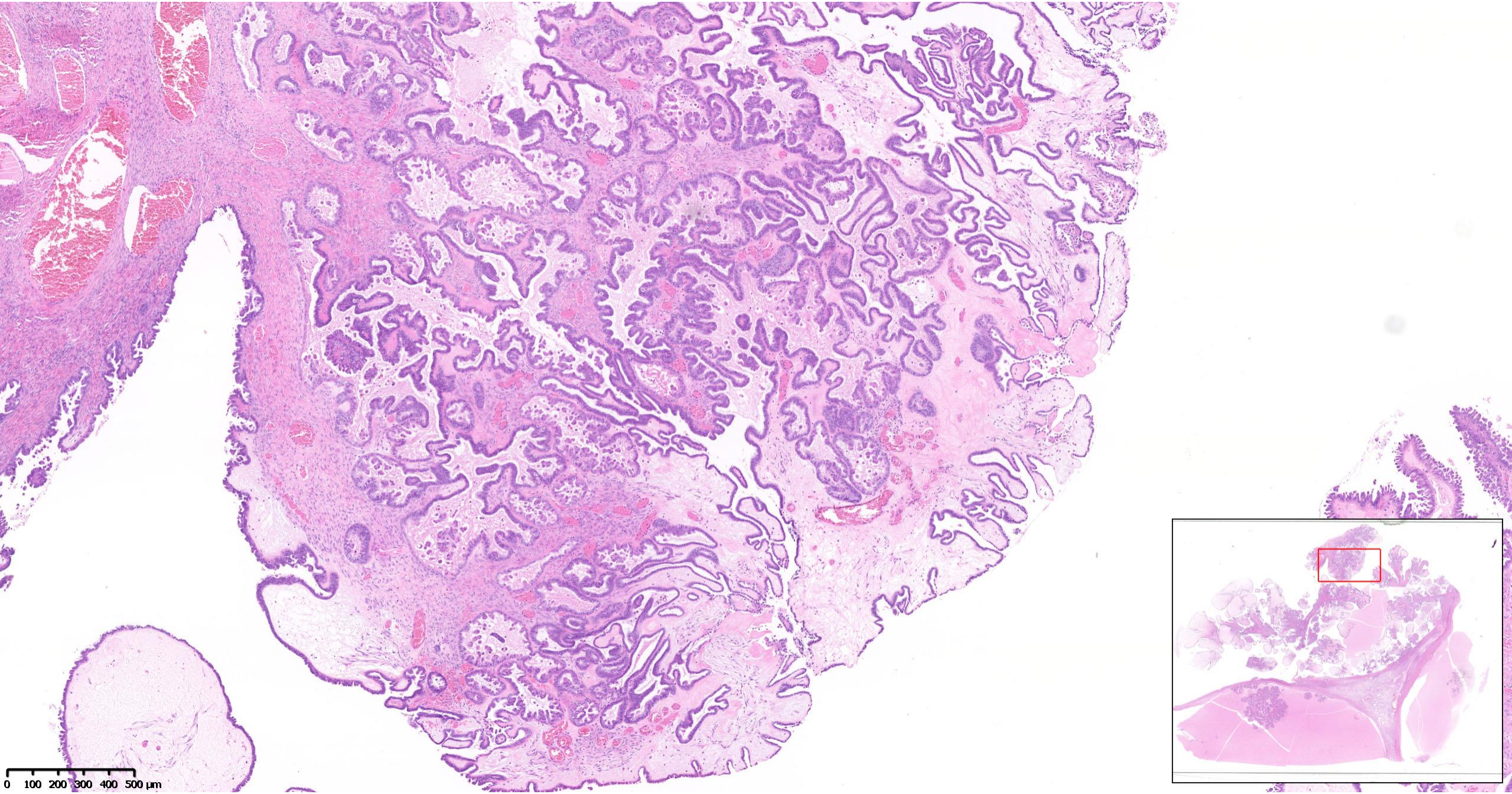
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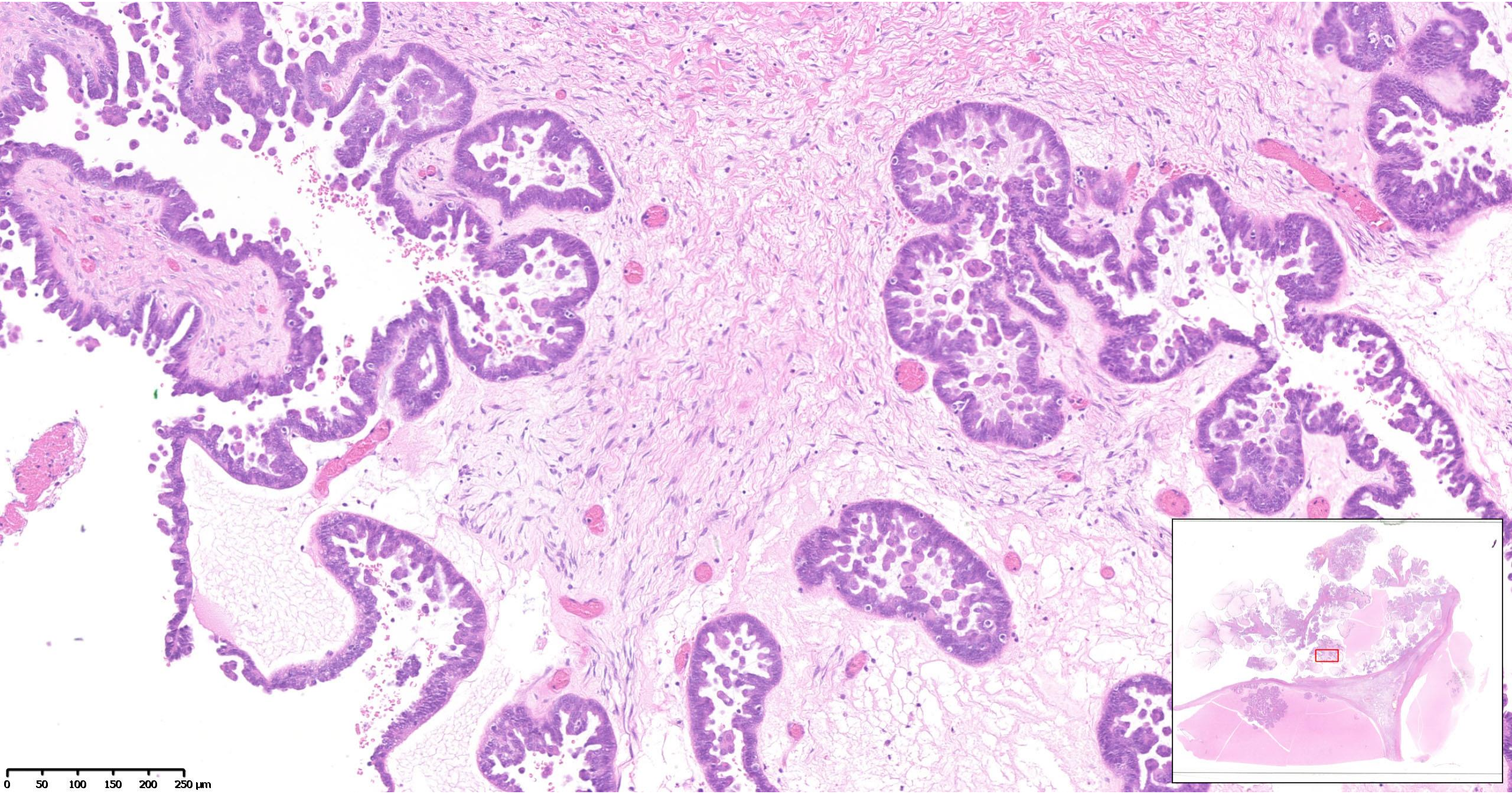
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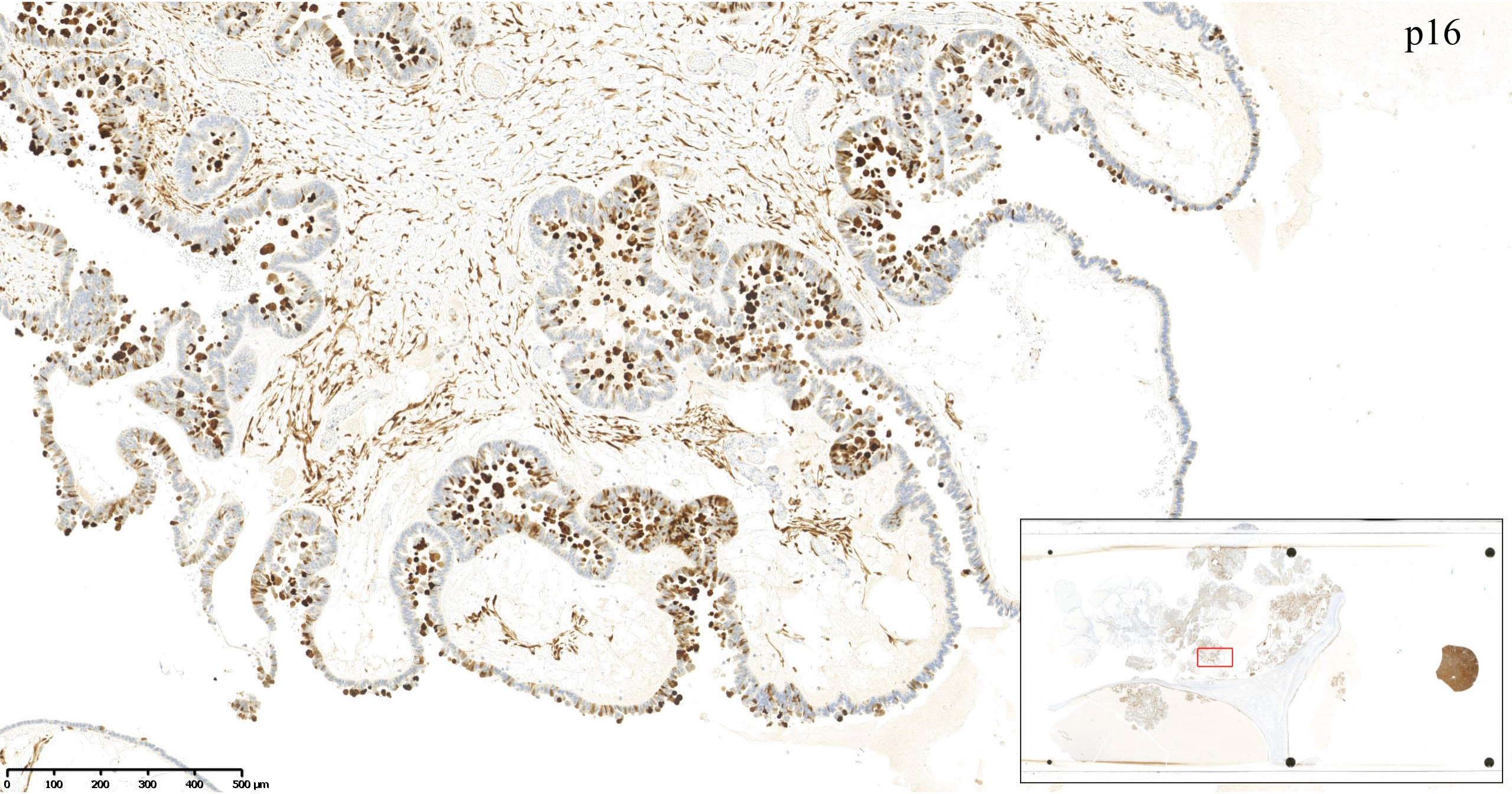

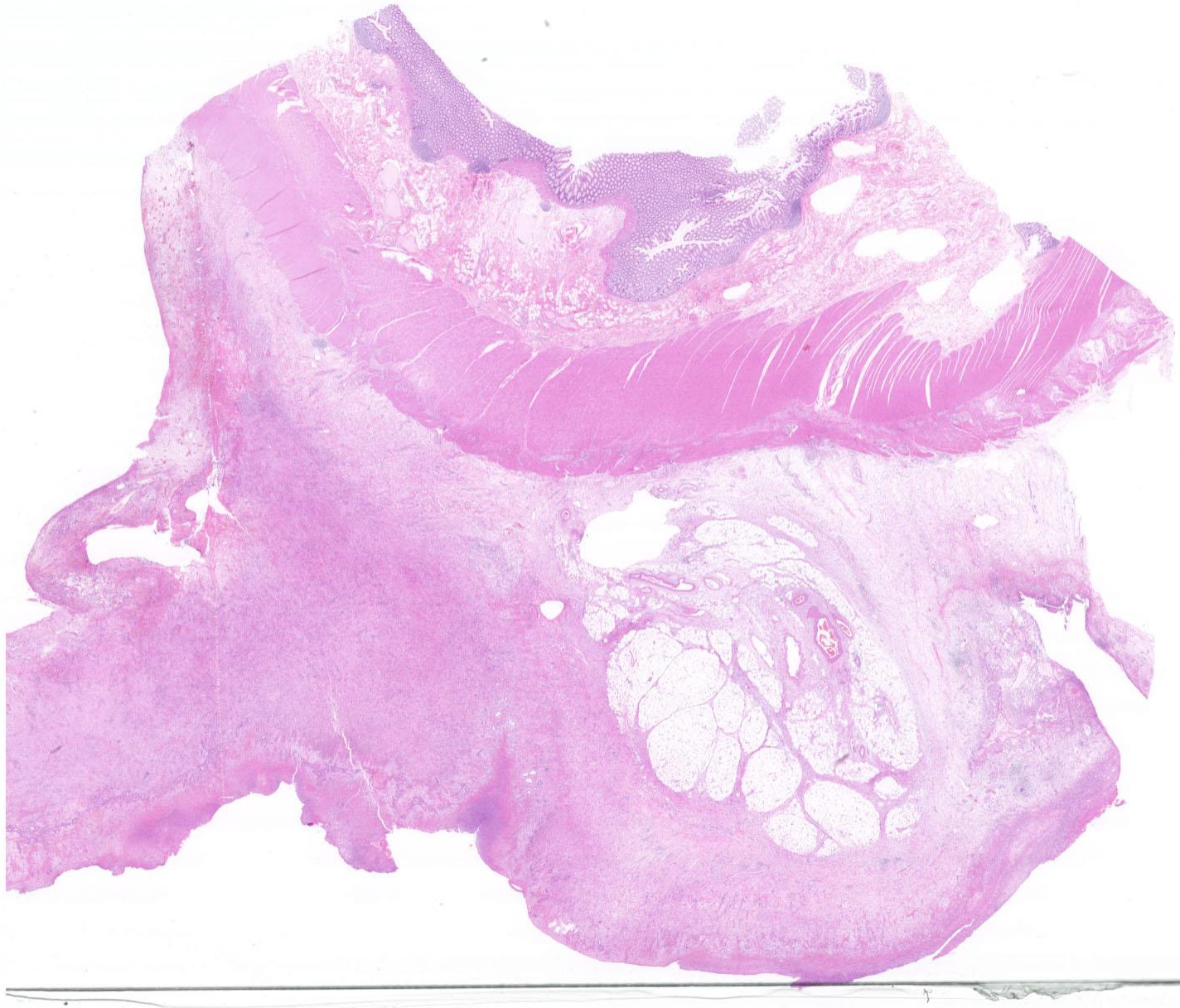

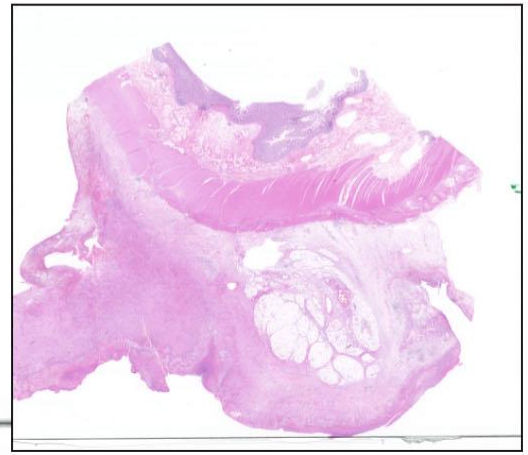

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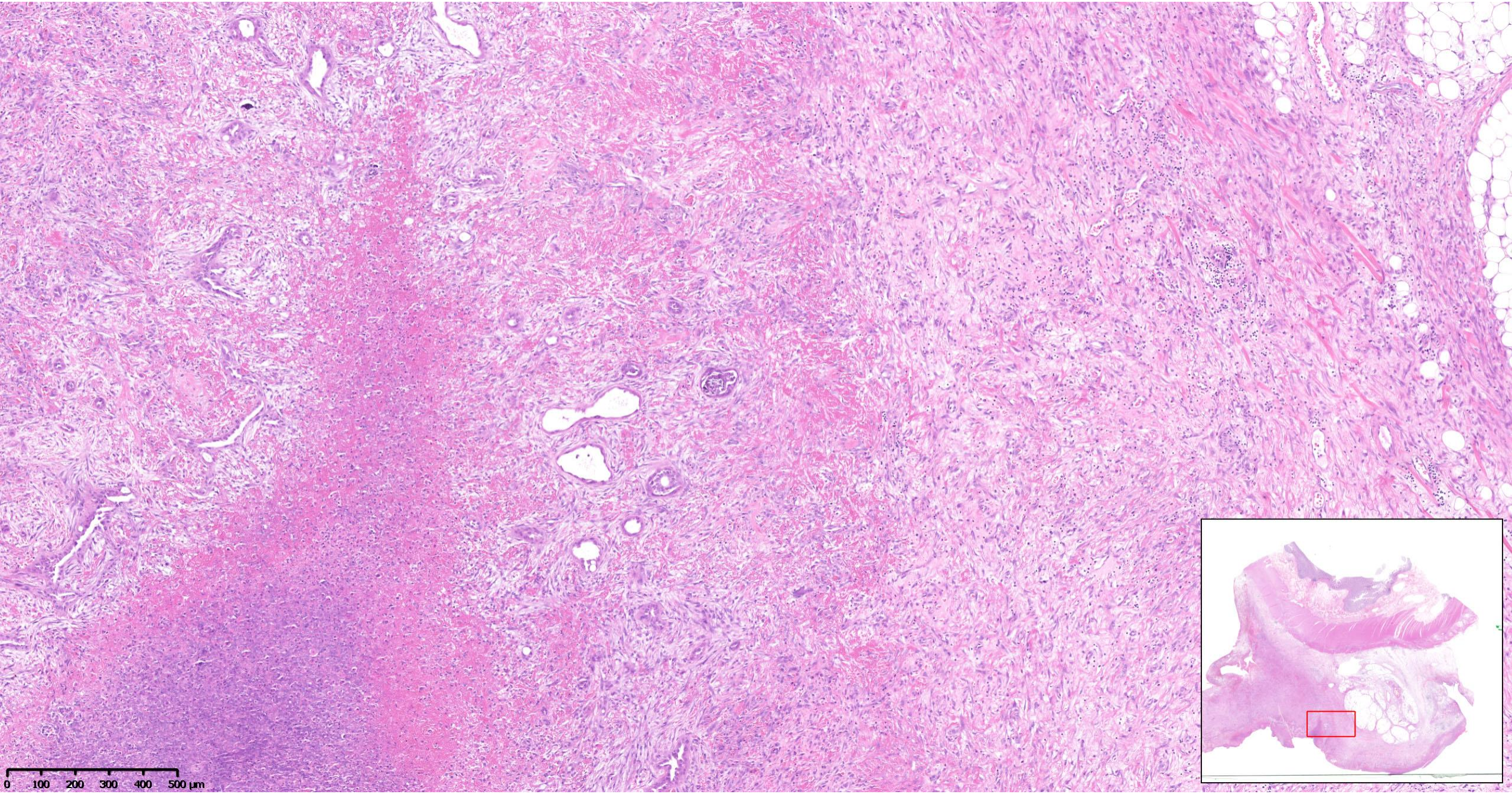
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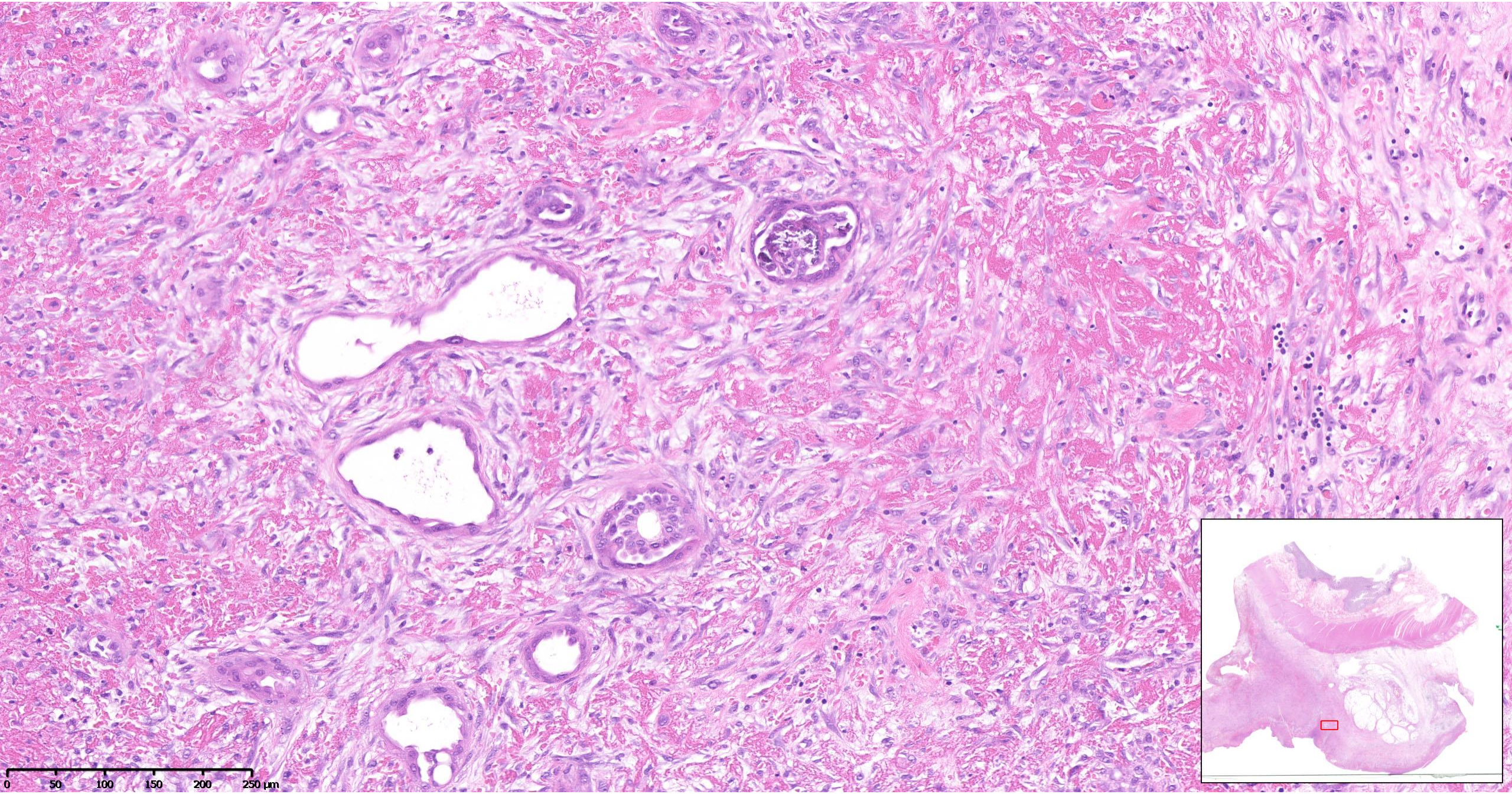
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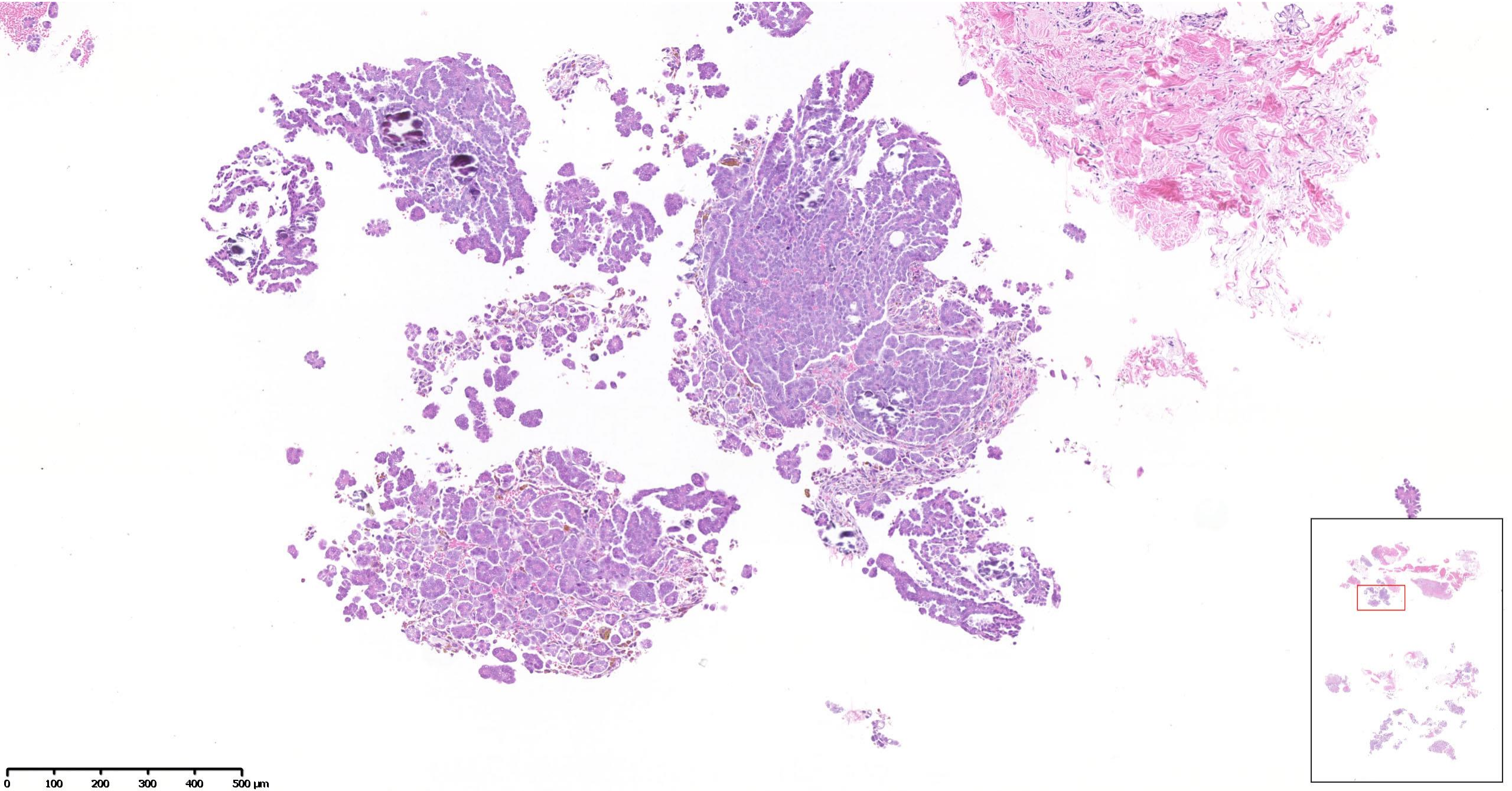
Diagnosis

Serous Borderline Ovarian Tumour with Non-Invasive Desmoplastic Implants

Case

- Female aged 28
- Multiple peritoneal nodules on CT and complex ovarian mass
- Biopsy from right chest wall lesion
- Numerous tiny fragments of tissue measuring 10 x 10 mm in aggregate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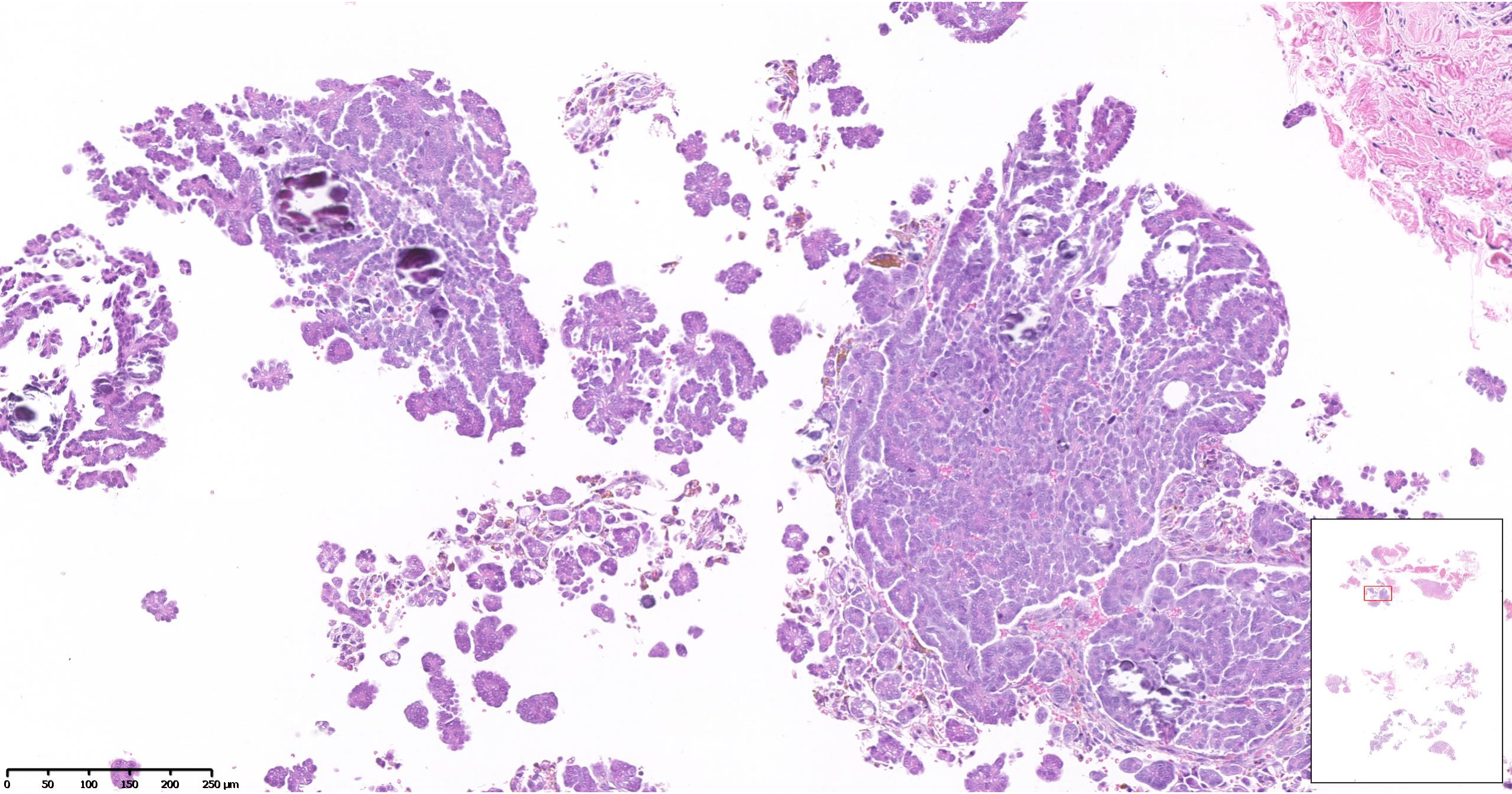
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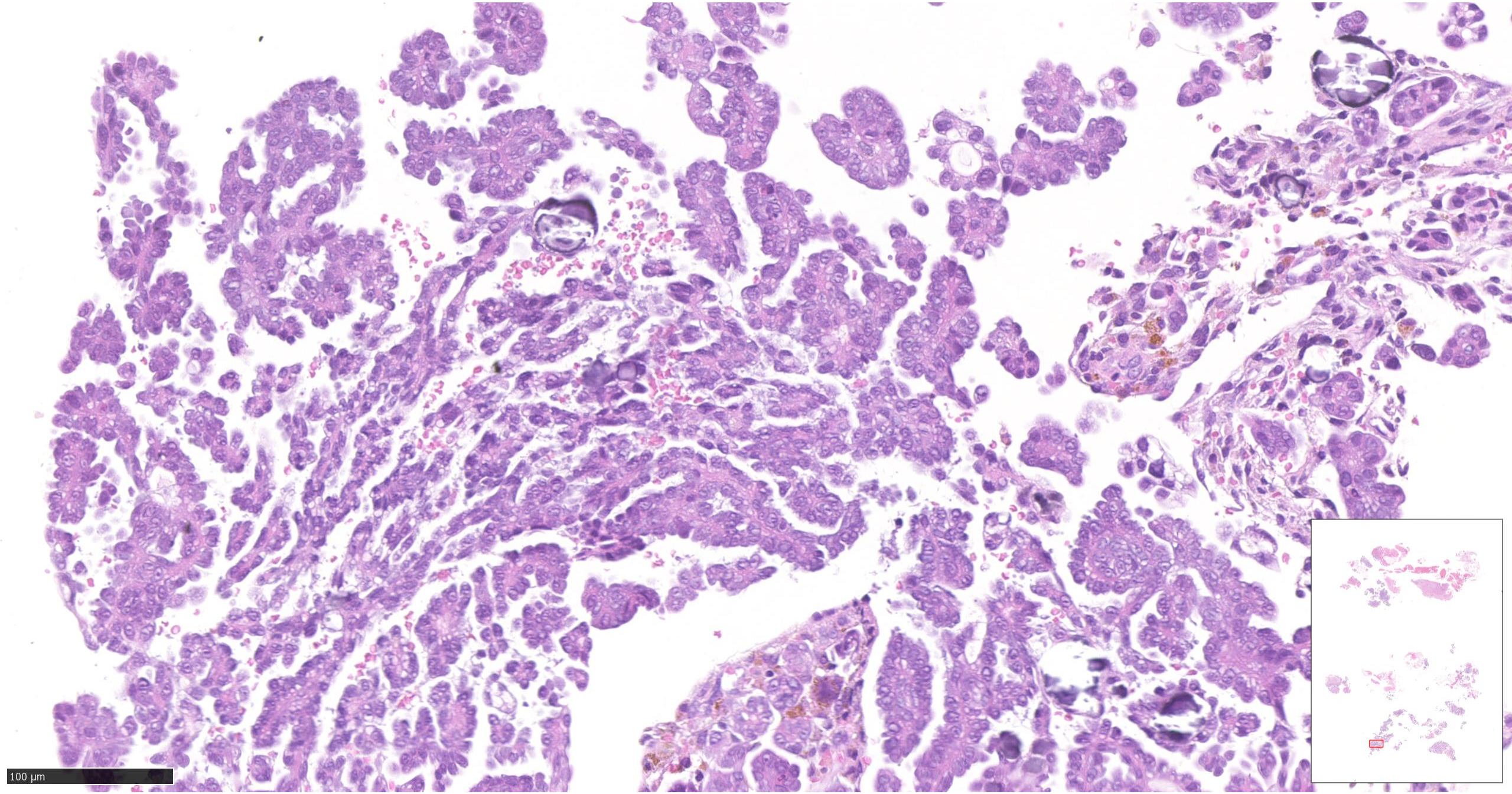
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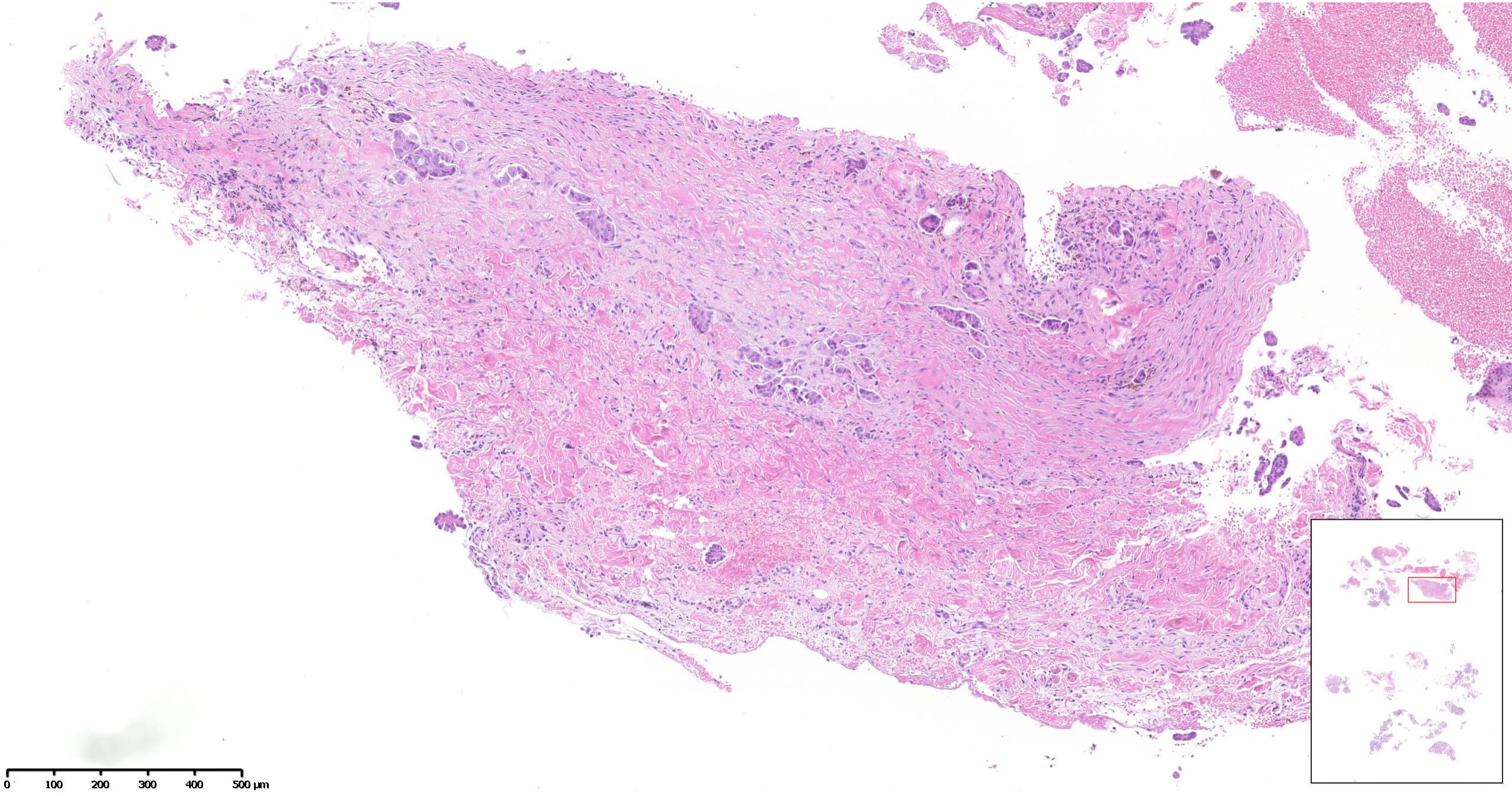
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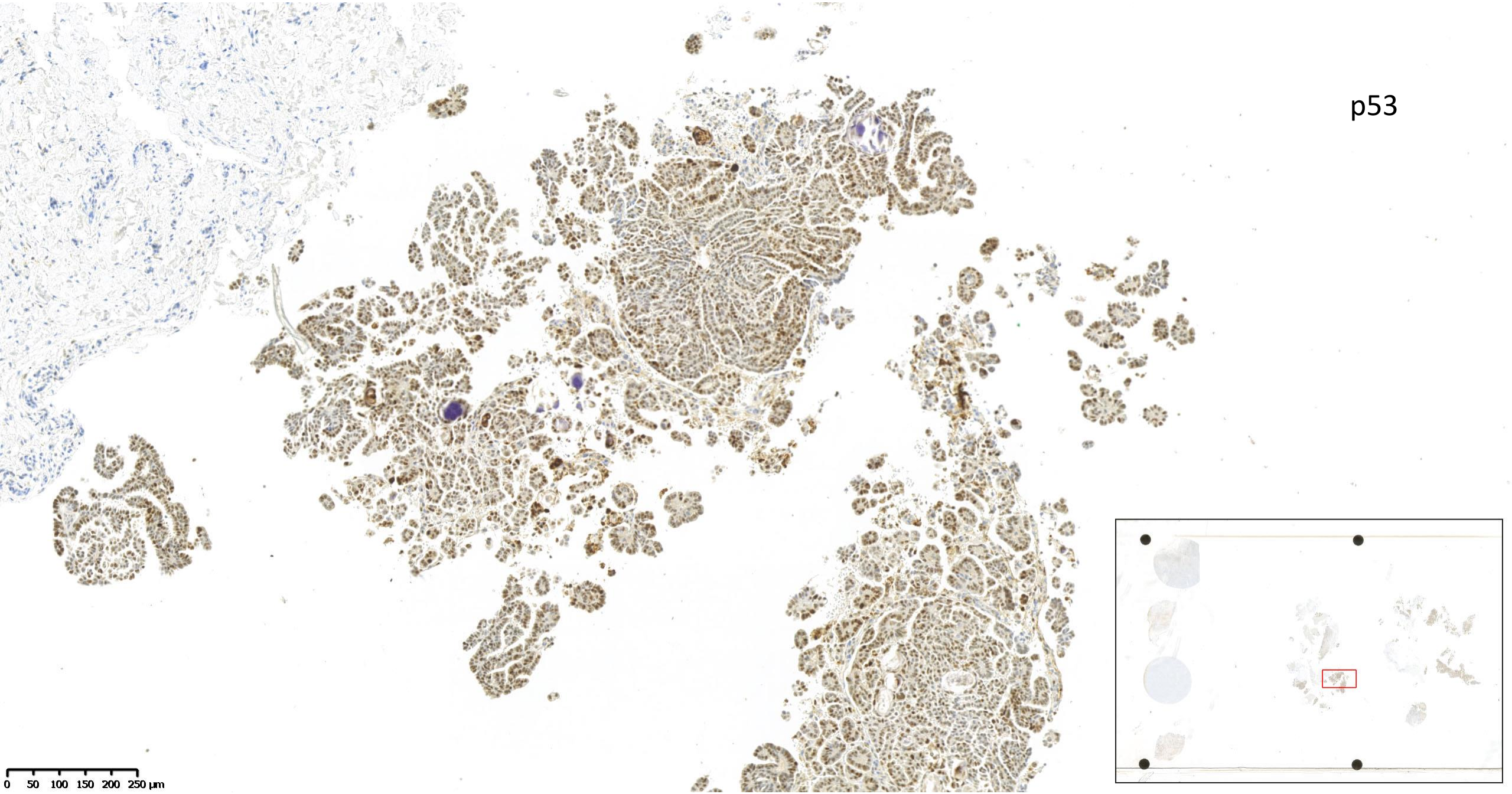
p53



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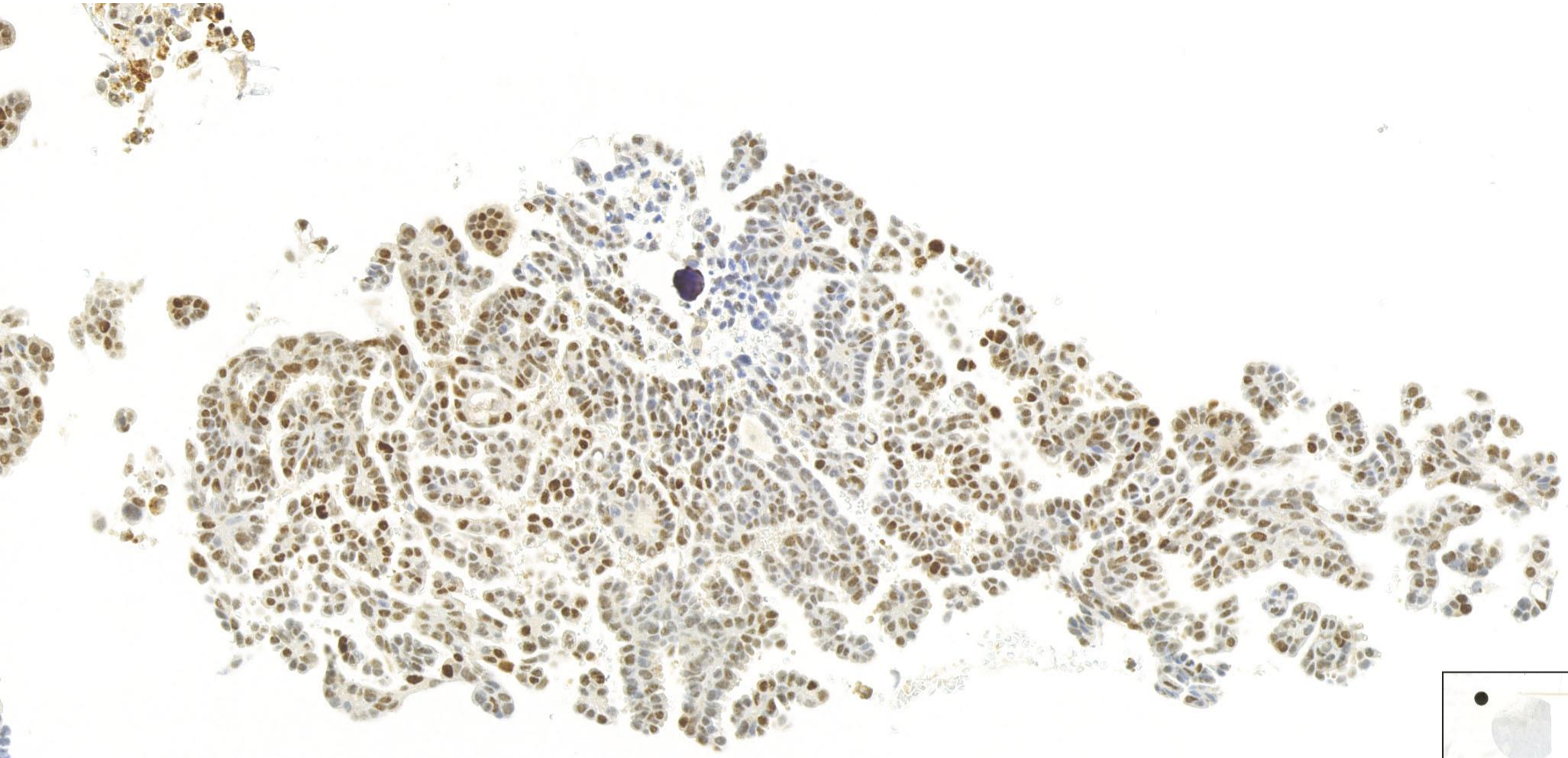


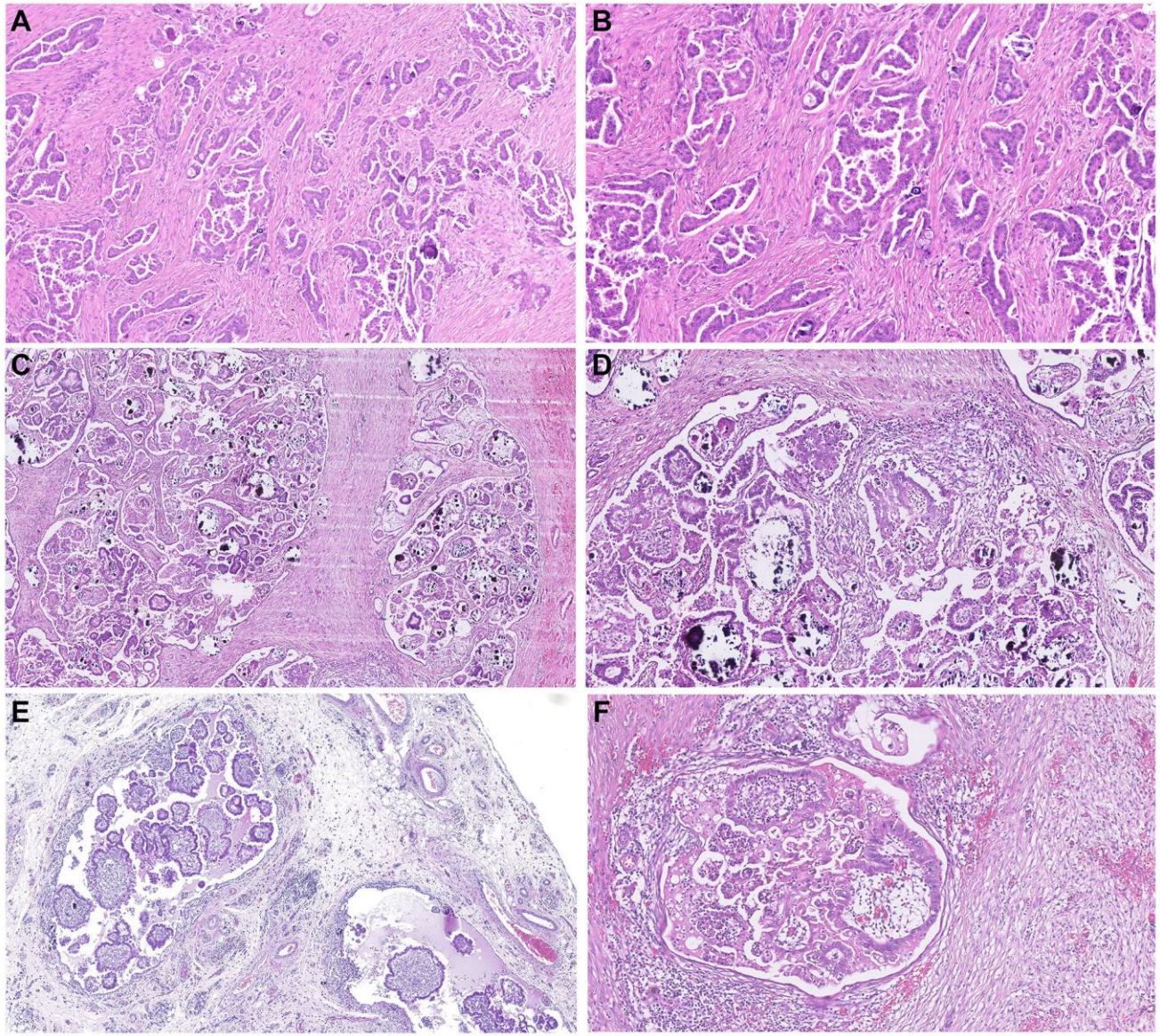
Diagnosis

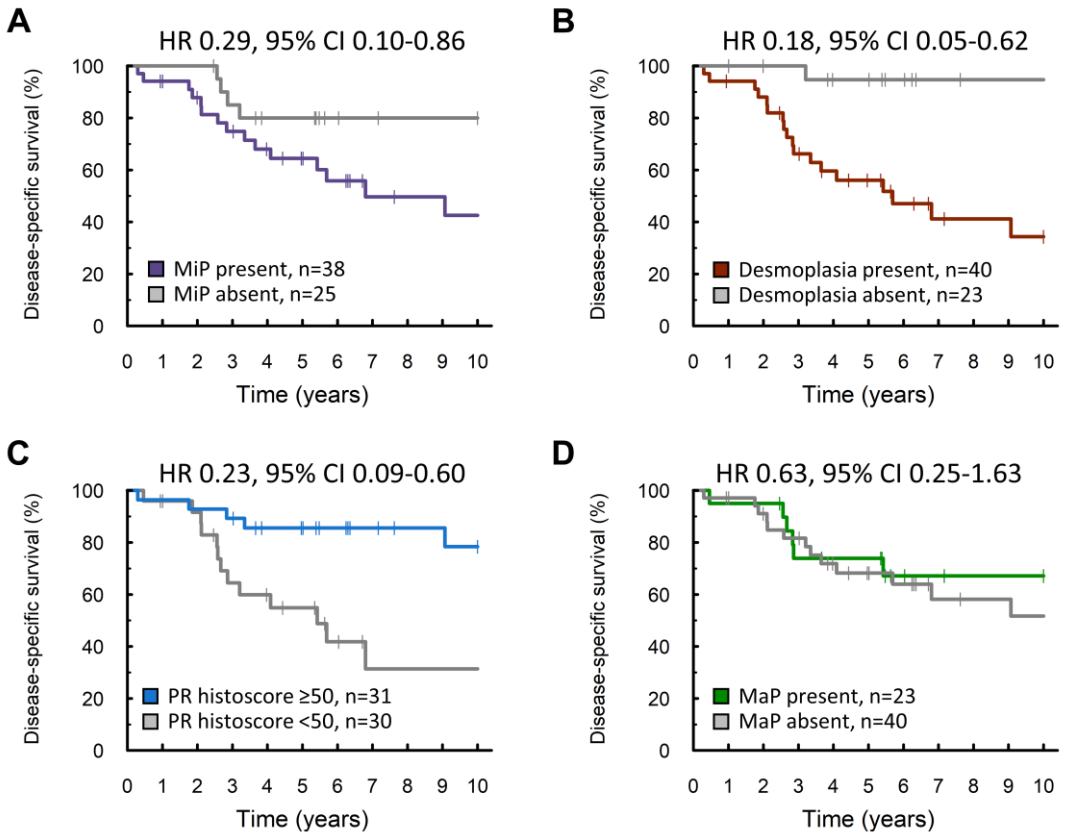
Low-grade Serous Carcinoma

Low Grade Serous Tumours

- *BRAF* and *KRAS* mutation common in borderline and invasive tumours (60-65%)
- *TP53* mutation absent and usually diploid
- Fewer karyotypic and other molecular abnormalities than high-grade tumours
- Diagnosis
  - Two-tier grading system based on nuclear atypia alone
    - Malpica A et al Am J Surg Pathol 2007; 31: 1168-74
  - WT1/p53 immunohistochemistry useful but DNA sequencing may be required
- Treatment
  - Differences in chemosensitivity
    - Santillan A et al Int J Gynecol Cancer 2007; 17: 601-606
  - Emerging role for MEK inhibitors (e.g. trametinib)
    - Gershenson DM et al Lancet 2022; 399: 541-553

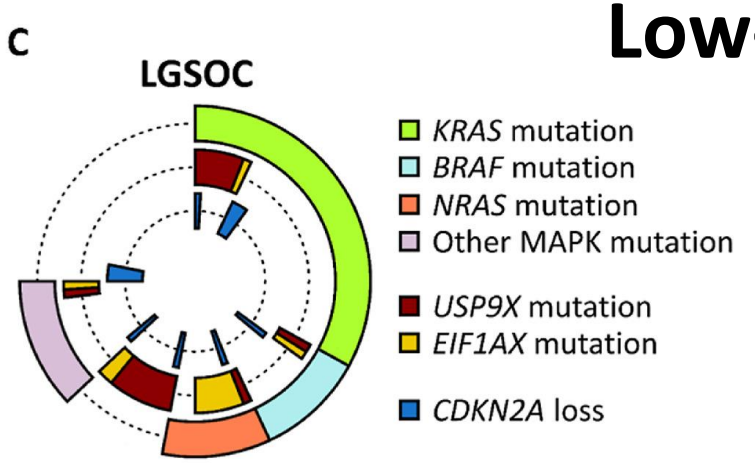
Low-grade Serous Carcinoma



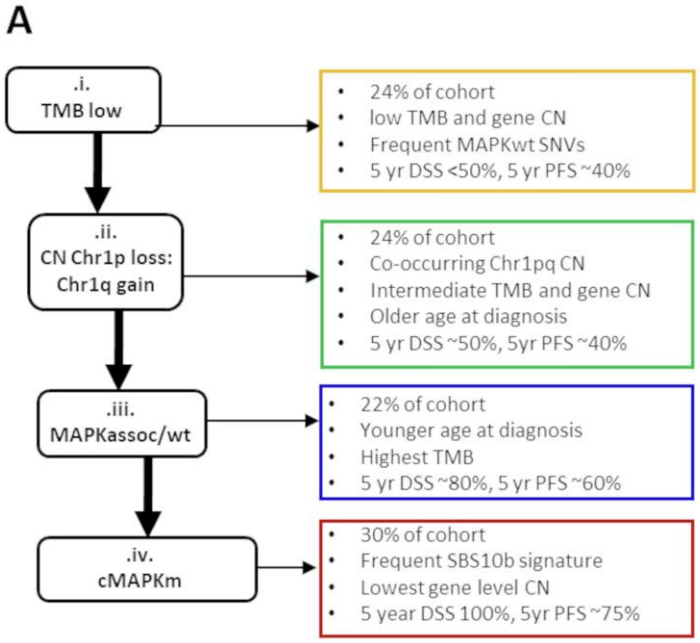


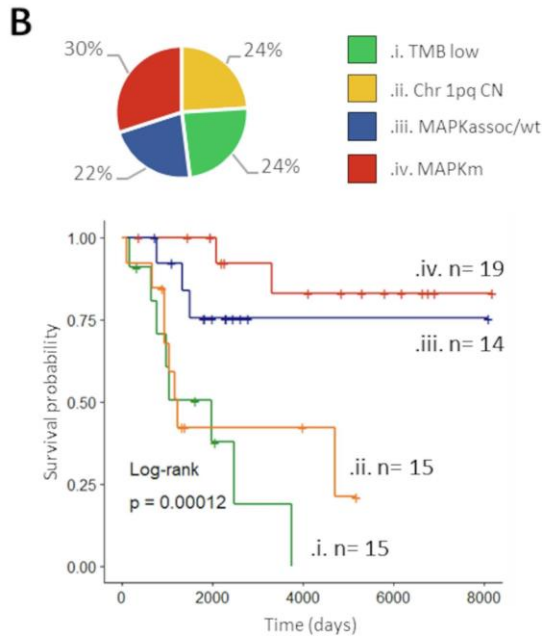
Hollis et al, Sci Rep 2023; 13: 7681

Low-grade Serous Carcinoma

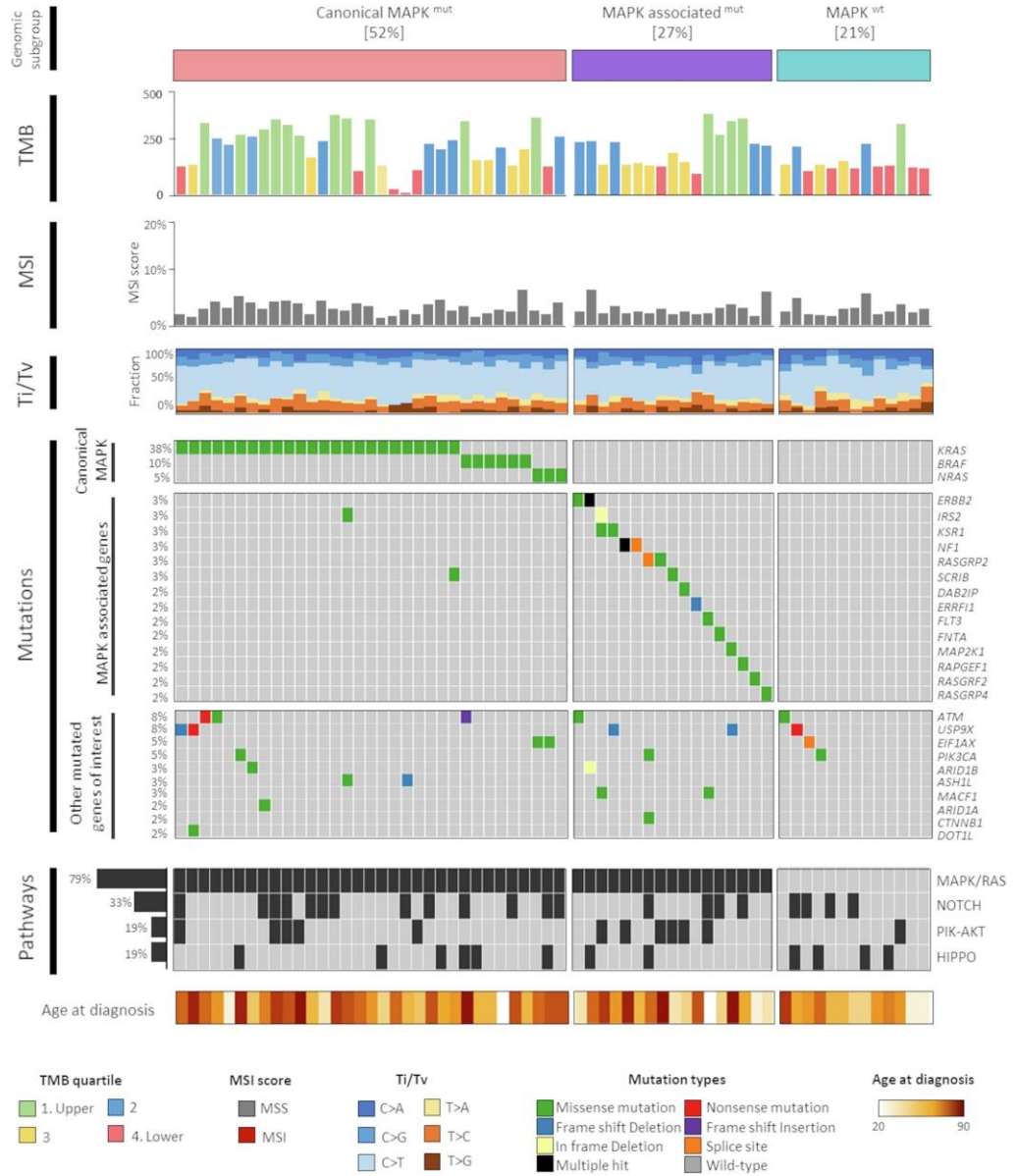


Hollis RL. Cancer Lett 2023; 555: 216057





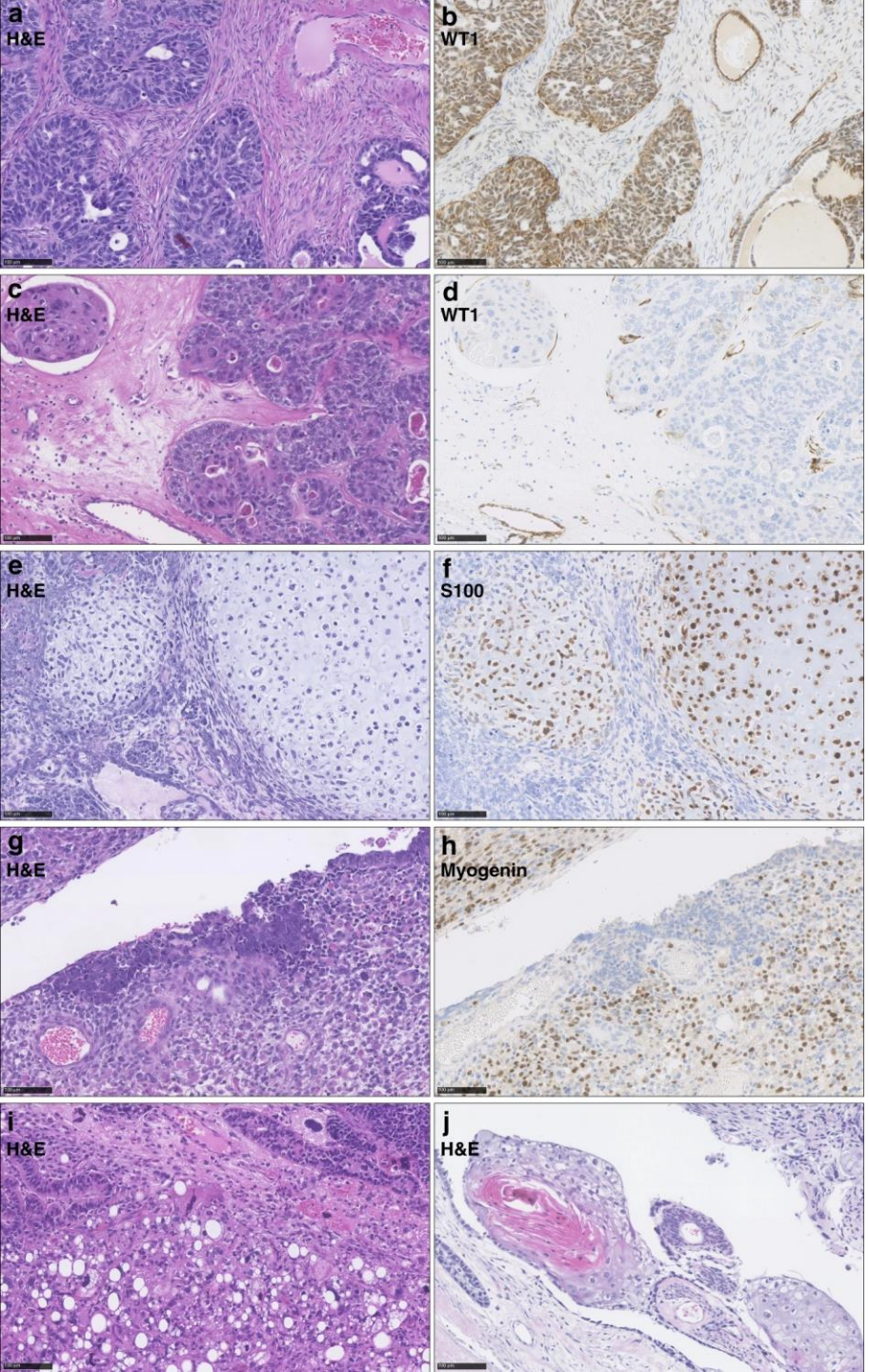
Thomson et al, Gynecol Oncol 2023; 174: 157-166



High grade transformation of low grade serous carcinoma?

- Some evidence but rare
- Requires rigorous morphological and molecular assessment
- More work needed at the interface between low grade and high grade serous carcinoma
  - *TP53* wild type high grade serous carcinoma?
  - High grade transformation of low grade serous carcinoma without *TP53* mutation?
- Important to avoid diagnostic and clinical confusion

Garg K et al. Int J Gynecol Pathol 2012; 31:423-8
Boyd C & McCluggage WG. Am J Surg Pathol 2012;36:368-75
Strickland AL et al. Int J Gynecol Pathol 2023;42:241-246

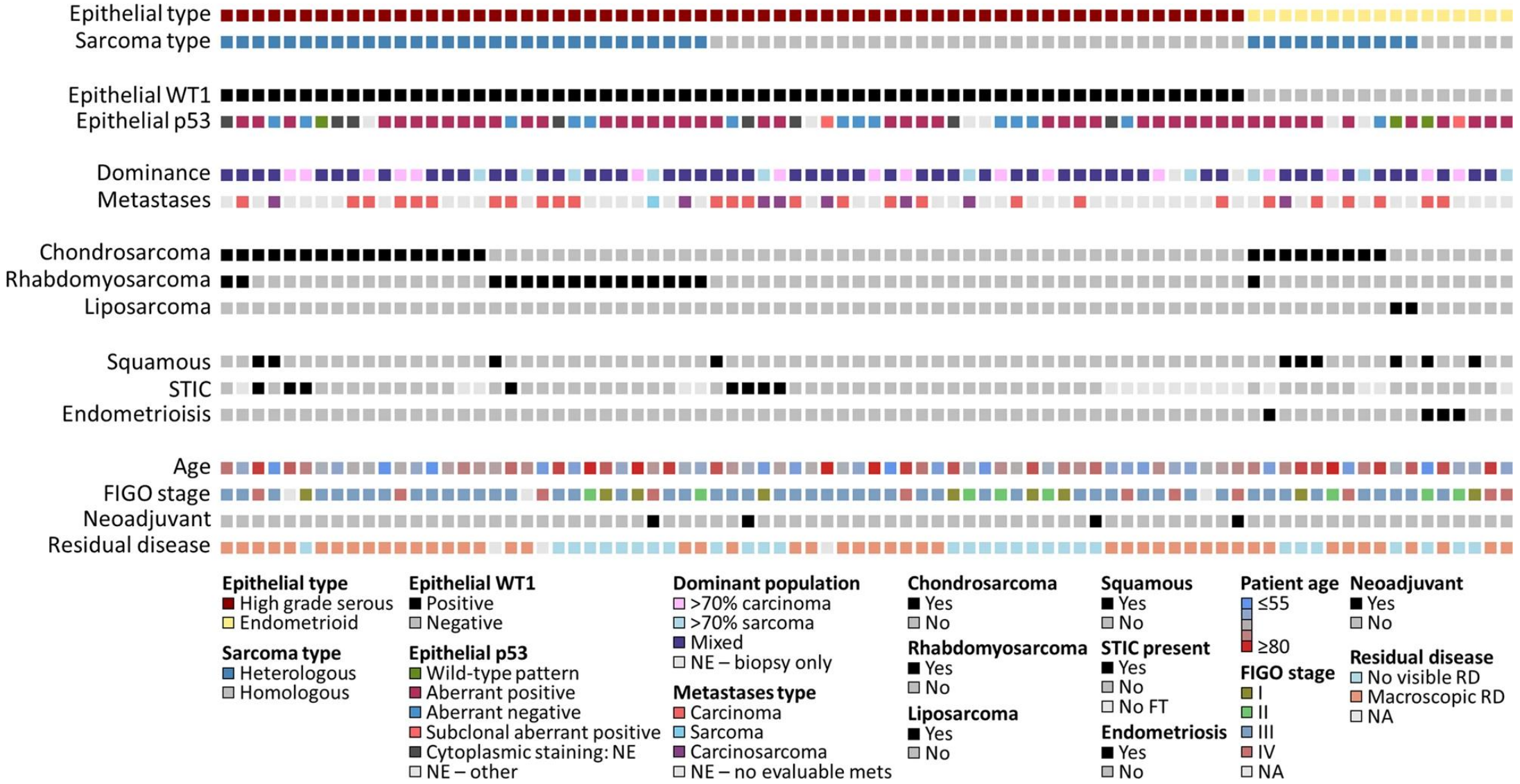


Carcinosarcoma

- Not just high-grade serous carcinoma with a sarcomatous component
- Associated with poorer outcome than high-grade serous carcinoma, independent of epithelial type
- Can molecular features help to predict more aggressive behaviour in endometrioid and high-grade serous carcinomas?

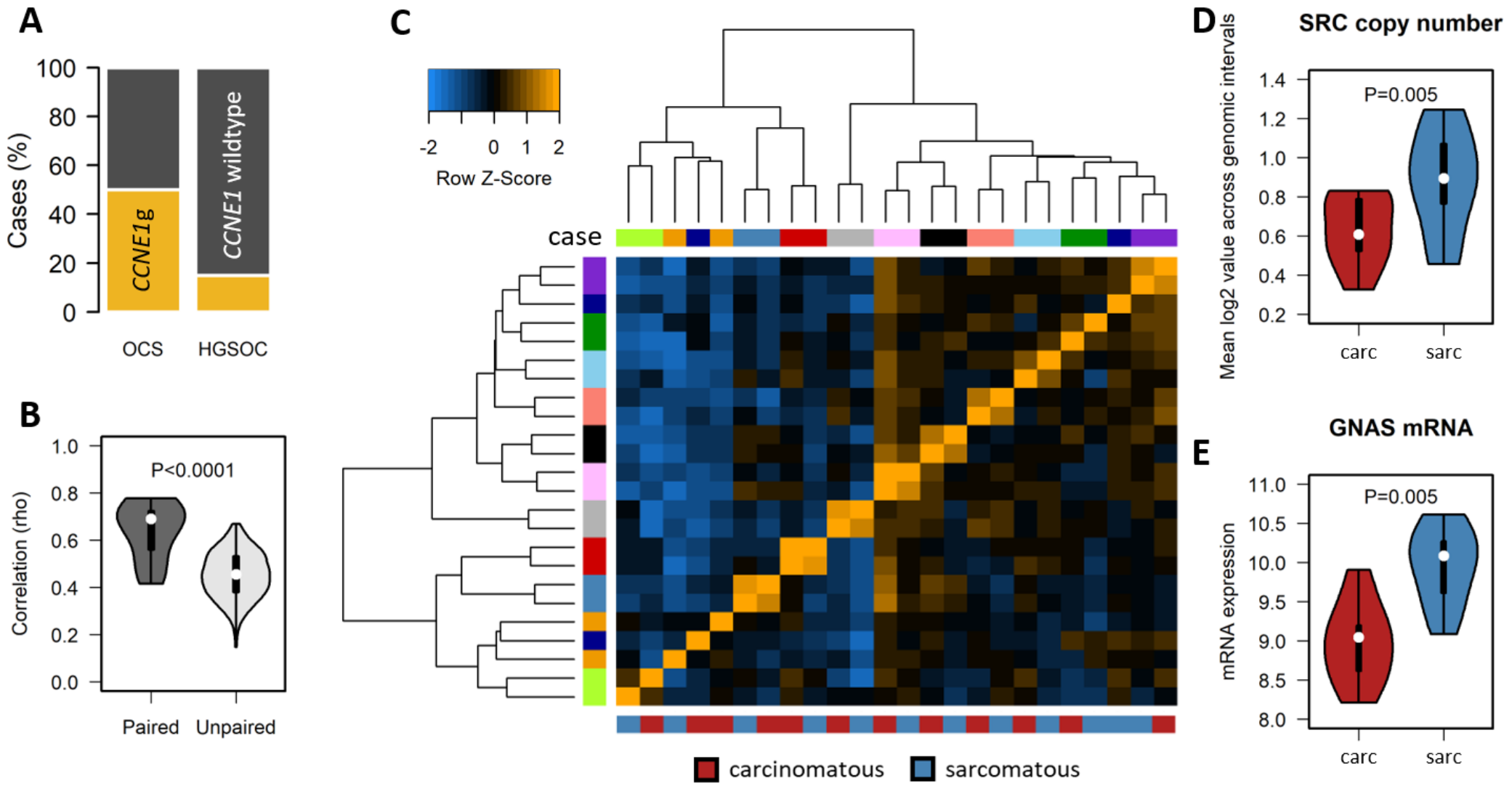
Hollis RL et al. Br J Cancer 2022; 127: 1034–1042

Carcinosarcoma



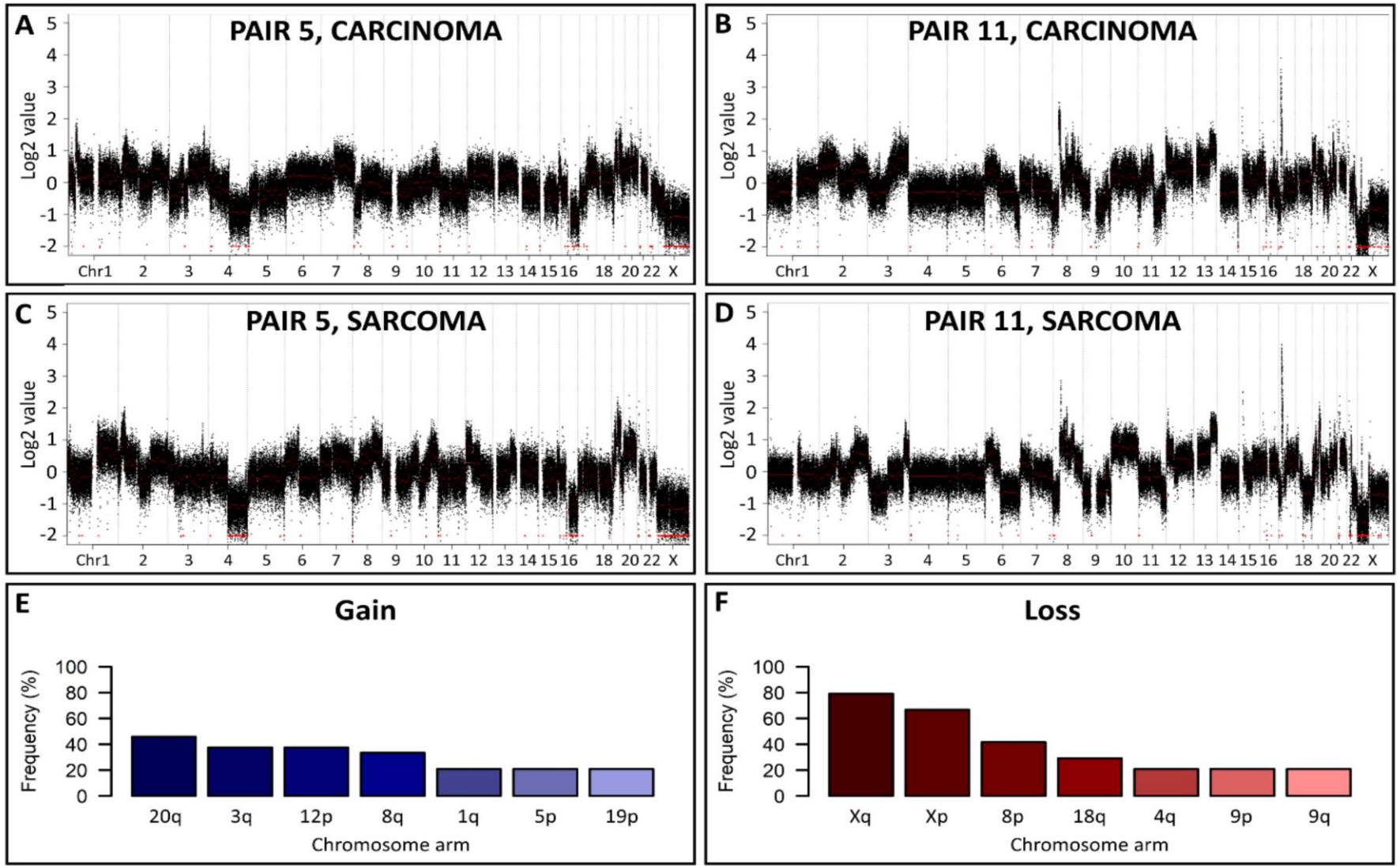
Hollis RL et al. Br J Cancer 2022; 127: 1034–1042

Carcinosarcoma – Copy Number Alteration



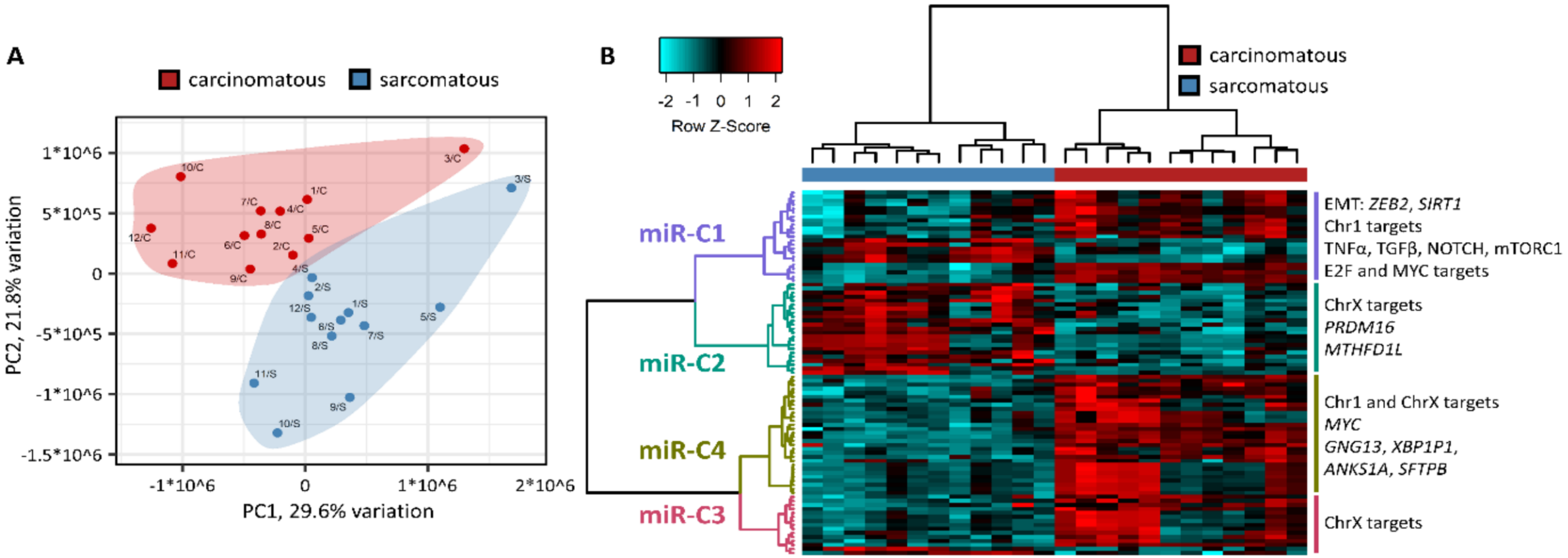
Herrington CS et al. Br J Cancer 2024; 130: 327-335

Carcinosarcoma – Copy Number Alteration



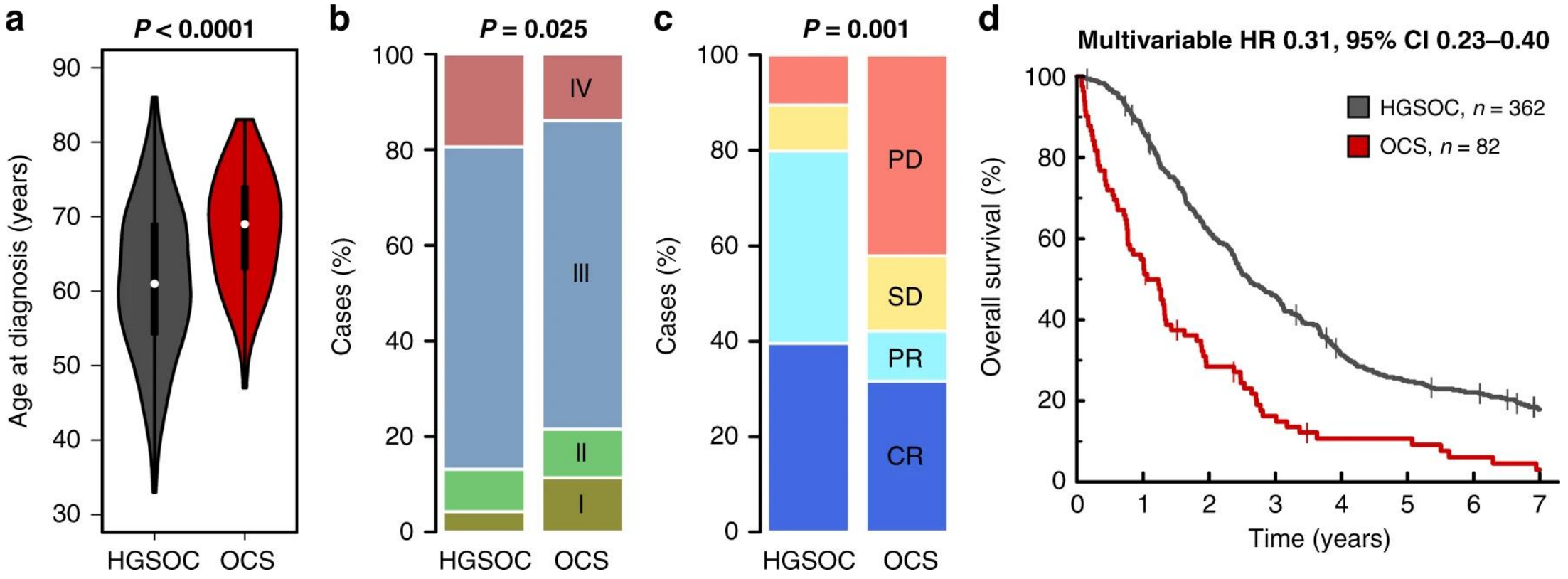
Herrington CS et al. Br J Cancer 2024; 130: 327-335

Carcinosarcoma – microRNA Analysis



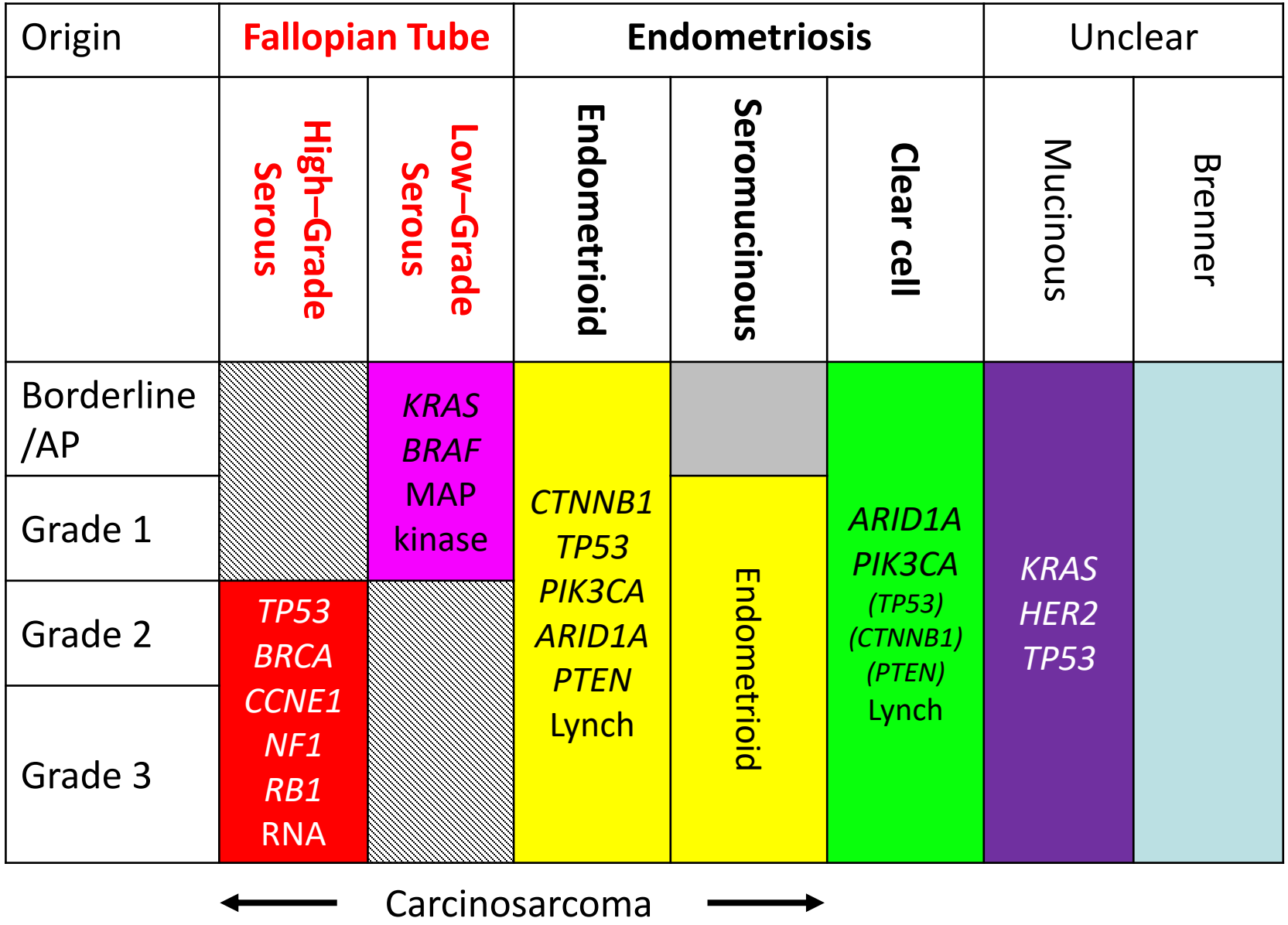
Herrington CS et al. Br J Cancer 2024; 130: 327-335

Carcinosarcoma vs High-Grade Serous Carcinoma



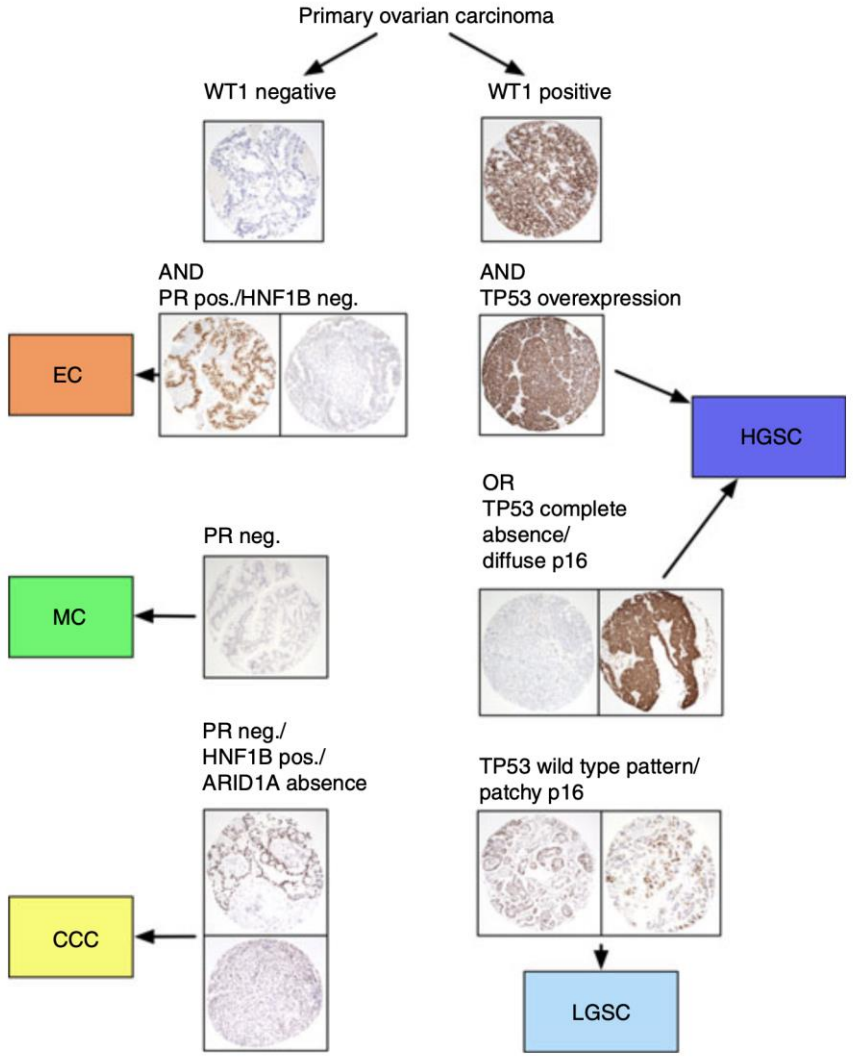
Hollis RL et al. Br J Cancer 2022; 127: 1034–1042

Ovarian Epithelial Tumours



Future Directions

- Improved accuracy of primary diagnosis
- Improved stratification within tumour types for therapy
- Development of novel therapies based on improved understanding of tumour type and stratification



Antibody-Drug Conjugates

- A range of targets – HER2, FRα (FOLR1), TROP2, CD30 etc
- Mirvetuximab soravtansine-gynx
  - FDA approved for FRα-Positive, Platinum-Resistant Ovarian Cancer
  - FOLR1 IHC as companion diagnostic

Dumentet et al, Nat Rev Drug Discov 2023; 22: 641-661 (ADC review)
Dilawari et al, Clin Cancer Res 2023; 29: 3835-3840 (FDA approval summary)
Bogani et al, Int J Gynecol Cancer 2024; 34: 469-477 (Clinical review)

nicola murray foundation

Target Ovarian Cancer

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